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THE LATE EFFECTS OF WAR NEPHRITIS[1]

BY W. E. HUME AND F. J. NATTRASS

(From the Ministry of Pensions Hospital, Newcastle-on-Tyne)

THE purpose of this paper is to give some indication of the present state of men who suffered from acute nephritis during the War. Little definite information on this subject has yet been published, and our observations lead us to think that too light a view has hitherto been taken as to the late effects of the disease.

The most authoritative record in this country was published by S. C. Dyke (1) in April 1922. He concluded that complete recovery had occurred in 70 per cent. of 100 cases which he observed personally in France, and whose subsequent histories he traced with the help of the Ministry of Pensions records: 3 per cent. of these cases had died.

G. L. Thornton (2), in 1923, gave details of the clinical and urinary findings in 100 cases under observation by medical boards. As regards capacity for work he estimated that 20 had very slight incapacity, 49 slight to moderate, 17 considerable incapacity, 8 incapacity for any but the lightest occupation, and 1 total incapacity. One case of the 100 died during the period of observation, and in the remaining 4 the capacity for work was uncertain. These figures seem to imply that about 10 per cent. had severe renal disease.

Such information as is available from French and German sources shows wide differences in the conclusions arrived at. Giroux (3), in 1919, examined 31 cases after an interval of two to three years from the acute illness: he found persistent albuminuria in all the cases and raising of blood-pressure in the majority. This author quotes P. Merklen and L. Desclaux, who found 77 per cent. of cases still uncured one year after apparent recovery from the acute phase: of these cases 65 per cent. appeared to be improving, while 35 per cent. showed evidence of progressive disease.

Siguret (4), in 1923, reported the results of an inquiry into 47 cases of war nephritis; 3 cases had apparently made a perfect recovery, while 5 others, though the urine was free of albumin, showed slight renal defect by various tests; 22 patients showed evidence of mild but definite chronic nephritis, and 15 had advanced disease. The remaining 2 cases had died of severe chronic nephritis.

[1] Received March 11, 1927.

Schirokauer (5), in 1920, traced 26 cases out of 200 whom he had seen in the acute attack in France. Of these 26 cases, 2 had died, and of the remaining 24, 22 showed no protein, casts, or blood-cells in the urine; further, there was no raising of blood-pressure in any of these cases except in 2 elderly men. Schirokauer admits that these figures are inconclusive and thinks that the prognosis is, on the whole, much the same as in peace nephritis. This author also quotes Schlayer, who concluded that 4·4 per cent. of his cases had completely recovered and 49·6 per cent. had partially recovered.

Deutsch (6), writing in 1921, gives more definite figures, viz. 49·5 per cent. complete recoveries and 21·5 per cent. partial recoveries. The remaining 29 per cent. showed evidence of severe damage to the kidneys.

Our observations were made during the years 1922 to 1925 at a Ministry of Pensions Clinic in Newcastle. The clinic was attended by nearly all the men in this district receiving pensions for alleged renal disease. No doubt a good many men who had acute nephritis in the Service were not invalided or have made no claim for pension: it is impossible to estimate the number of such cases, but it seems unlikely that the number is large, and the figures obtained at the clinic represent fairly accurately the results of the disease up to the present time.

The clinic was attended by 418 men. Of these 281 were selected in whom the history and documents indicated the occurrence of primary acute nephritis during the War. The acute illness occurred in France in 232 cases, in England in 25 cases, and in other parts of the war area in the remaining cases. A history of trench fever in association with the acute nephritis was given in only 3 cases, and in 3 cases the condition arose as a complication of scarlet fever. Chief stress was laid in selecting the cases upon the patient's story of the original illness. As a rule the account of the early symptoms was so clear as to leave no doubt in the mind of the observer that the patient had been the subject of acute nephritis. A typical case-history was as follows:

R. J. S., an onsetter in a coal-mine, joined the R.F.A. in October 1915, being passed A 1. He went to France in November 1916. In February 1917 he felt suddenly listless and had pains in the back and legs, and severe occipital and frontal headache. For 24 hours or more he was unable to pass any urine, and then he began to pass small amounts of blood-stained urine with much pain on micturition. At the same time his face and ankles swelled and the swelling lasted about 2 weeks. He was sent to England, where he was in hospital for 14 months. He was then returned to light duty, but a week later was back in hospital with a return of urinary symptoms, and he was discharged from the Army in 1918.

Unless a sufficiently characteristic story of acute nephritis, such as the above, was obtained, with a previous record of normal health, the case was not accepted as one of true war nephritis. Cases in men over 35 at the time of onset were accepted with reserve, but in many of these the history was so clear as to warrant their inclusion without any doubt being felt.

The cases were examined every three months. On each occasion a routine clinical examination was carried out, with special reference to the cardio-vascular system and ocular fundi. The urine was examined for protein by the salicyl-sulphonic test, and the amount of protein present graded according to the density of the precipitate into five groups, A, B, C, D, and E. E represented a slight but distinct trace, while A indicated that the urine was loaded with protein. The centrifugalized deposit was examined microscopically. Finally, the urea concentration test of MacLean and de Wesselow was carried out, and the urinary diastase estimated. Blood-urea estimation was not done as a routine.

Analysis of the results shows that the cases may be divided into three groups. In the first place, of the 281 cases, 128 or 45·5 per cent. show no definite evidence of any renal disease on repeated examination on the lines indicated. In many of these cases traces of protein and occasional casts were found, but not so consistently as to provide evidence in themselves of a renal lesion. The occasional finding of red blood-cells or pus-cells was also disregarded if unaccompanied by other abnormal signs. Some of these men are still in receipt of pension, but it is given rather for general debility and neurasthenia than for actual nephritis.

The second group consists of 27 cases, or 9·5 per cent., who have developed advanced renal disease, i. e. of a degree of severity requiring an assessment of disability of 70 to 100 per cent. Of these cases 7, or 2·5 per cent. of the total number, have died as the direct result of chronic nephritis; all the deaths occurred in young men, the oldest being 33. A post-mortem examination was obtained in only one case, in which the appearances were typical of chronic parenchymatous nephritis.

The clinical features of the cases which are included in this group are best illustrated by quoting the record of one case.

J. S., miner, joined the Army in 1914, at the age of 23, and went to France in 1915. In December 1915 he had an acute illness characterized by weakness, breathlessness, and swelling of the face and abdomen. He was sent home to hospital, where he recovered, and was put on home service in February 1916. Later the same year he returned to France, but was readmitted to hospital in 1917 with symptoms similar to the first illness. When first seen at the clinic on 20.6.23 he complained of shortness of breath, swelling of the ankles and eyes, headaches, and dizziness. His general condition was good and there was no anaemia or oedema. There was no evident enlargement of the heart, but the radial arteries were thickened and the blood-pressure was 160 systolic and 80 diastolic. The urine was loaded with albumin, and the deposit contained granular and hyaline casts, and a few red cells and pus-cells. The urea concentration test gave a reading of 1·6, and the diastatic index was 20. In seven subsequent examinations the urine remained loaded with albumin, and the urea varied from 1·2 to 1·8. Six consecutive diastase estimations read 20, 6·6, 2·0, 20, 20, 20. Casts, red cells, and pus-cells were found every time. In January 1925 the blood-pressure had risen to 210 systolic and 125 diastolic, and there were small

haemorrhages and cotton-wool patches in the right fundus. The last entry records his admission to hospital in April 1925 with severe general oedema.

In Table I a summary is given of the findings in the 27 cases to indicate the evidence upon which the diagnosis of advanced nephritis was based.

TABLE I.

Summary of Findings in 27 Cases of Advanced Chronic Nephritis.

Raised blood-pressure	27 cases = 100 %
Persistent protein	26 ,, = 96 %
,, casts	25 ,, = 93 %
,, blood	23 ,, = 85 %
,, pus	20 ,, = 74 %
Low urea concentration	21 ,, = 78 %
Low diastase	18 ,, = 67 %
Retinitis	10 ,, = 37 %

The evidence of disease in all the cases was gross: the amount of protein was usually large, and the blood-pressure was always considerably raised. The last recorded pressures in the 27 cases ranged from 240/150 to 150/90. 75 per cent. of the cases had systolic pressures of over 170, and in only 2 cases was the diastolic pressure below 100: one of these two had a positive Wassermann. 37 per cent. of these cases had renal retinitis with or without optic neuritis.

The third and last group contains 126 cases, or 45 per cent., who show, in our opinion, evidence of gradually progressive renal disease. There is more possibility of error in the inclusion of cases in this group than in the other two, as there is considerable scope for difference of opinion as to the value of the evidence available. The degree of renal damage in the cases composing the group varies very much. Some approach closely to the second group already considered and classified as 'advanced'. In the majority the degree of renal damage is as yet moderate, but consideration of the individual records of the examinations shows sufficiently consistent deviations from the normal to justify the diagnosis of some degree of chronic nephritis. It is necessary to emphasize that chief stress has been laid on the consistency of the findings, since the result of single examinations might frequently have led to the conclusion that the kidneys were normal. It is difficult, for example, to be dogmatic as to the normal range of blood-pressure, but if frequent examination reveals figures above the average for the individual age, and this is combined with other evidences of renal disease, relatively slight but consistent, it appears justifiable to include the case in this group. Table II gives a summary of the evidence upon which the diagnosis was made in these cases.

TABLE II.

Findings in 126 Cases of Nephritis of Moderate Severity.

Raised blood-pressure	90 cases = 71 %
Persistent protein	98 ,, = 78 %
,, casts	58 ,, = 46 %
,, blood	40 ,, = 32 %
,, pus	55 ,, = 44 %
Low urea concentration	42 ,, = 33 %
Low diastase	42 ,, = 33 %

We conclude therefore that in this group of 45 per cent. there is some degree of permanent damage to the kidneys, and many of the cases must be expected in future years to develop severer manifestations of chronic nephritis.

The results in the three groups which we have described may be summarized as shown in Table III.

TABLE III.

Shows the Present Condition of 281 Cases who had Acute Nephritis during the War.

Group I.	No evidence of nephritis	128 cases	= 45·5%
Group II.	Advanced chronic nephritis	27 ,,	= 9·5%
Group III.	Gradually progressive nephritis	126 ,,	= 45·0%
	Total	281 cases	= 100·0%

Deaths (cases in Group II) 7 cases = 2·5 %.

Certain points of interest may be noted with reference to the investigation as a whole. In the paper referred to earlier, Dyke laid stress on the relation of the age of onset to the prognosis in his cases, the proportion of cases terminating in recovery within twelve months being slightly higher in men under 35 at the time of onset than in men over that age. In cases not recovered by the end of twelve months, the older men also showed a less favourable subsequent course.

As it happened we also selected this age, 35 years at the onset, to divide our cases into two categories. The result of an analysis from this point of view differs from that arrived at by Dyke. Of the men under 35 at the time of the acute illness, 43 per cent. fall into our first group (complete recovery), 45·8 per cent. fall into the second group (progressive nephritis), and 11·2 per cent. into the third group (advanced nephritis). Of the men over 35 at the onset, 52·6 per cent. are in the first group, 42·2 per cent. in the second group, and 5·2 per cent. in the third group.

So far, therefore, as our cases are concerned, it appears that the older men have made a better recovery than the younger. This is rather surprising, and it is possible that the explanation lies in our approach to the subject differing from that adopted by Dyke. Dyke saw his cases personally in the acute phase and could therefore include with confidence cases which he observed in the older men; we were dependent upon history in selecting our cases, and therefore excluded a good many older men in whom we could not with reasonable certainty exclude pre-existing chronic disease at the time of the acute illness. On the other hand, Dyke drew his conclusions regarding prognosis from Ministry records, while our figures are based on personal examination in the later stages.

Considered in conjunction with the clinical findings, the urea concentration and diastase tests were found to be, on the whole, consistent, and of considerable value in estimating the degree of renal damage. In the severer cases impaired concentration of urea was found with great consistency, and a low diastatic index was fairly constant, though not invariable. On the other hand, in the

milder cases, in which help was particularly needed, the tests did not give much information, especially the diastase test. It is essential that these tests should be repeated several times before confidence can be felt as to their significance in indicating milder degrees of renal damage; this has been emphasized by McLean and de Wesselow in reference to the urea concentration test, where the factor of diuresis frequently vitiates the result. Our observations confirm the conclusion of McLean and de Wesselow, that low readings in the two tests may be found in normal individuals, but on the other hand normal readings are rarely found in the presence of nephritis of any considerable severity.

Raising of the blood-pressure, with the presence of albumin, casts, and blood-cells in the urine, remain the most important evidences of chronic nephritis, and after the diagnosis has been made on these grounds, the tests of renal efficiency are useful as confirmatory evidence and in helping to estimate the degree of renal damage. We rarely found more than a trace of albumin in the urine, and never a considerable amount, except in cases in which we were satisfied that a definite degree of nephritis existed.

The persistence of pus-cells in a large proportion of the cases is also of interest, and is probably correlated with the frequency and pain in micturition so commonly present in the acute phase: such symptoms were much more noticeable in acute war nephritis than they are in the disease as seen in civil life.

Summary.

1. Observations were made on 281 men who suffered from acute nephritis during the War.

2. Of these cases 45·5 per cent. now show no evidence of renal disease.

3. 9·5 per cent. of the cases have developed advanced chronic nephritis, and 2·5 per cent. have died of the disease.

4. The remaining 45 per cent. of the cases show evidence of some permanent damage to the kidneys, and are probably developing chronic nephritis.

5. The value of the urea concentration and diastase tests is discussed.

We are indebted to the Director-General of Medical Services, Ministry of Pensions, for permission to publish this article, and to Dr. P. C. W. Laws, who carried out the laboratory work.

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THE FASTING GASTRIC SECRETION IN MAN[1]

By W. MORRELL ROBERTS

(From the Department of Clinical Investigations and Research, Manchester Royal Infirmary)

THIS work was undertaken, in the first instance, in order to clear up one or two points which had arisen in an earlier investigation of the effect of atropine on gastric acidity (1), but it became apparent as the work progressed that the results obtained, in addition to affording information of the nature desired, threw some light on gastric secretion as occurring normally in man, which, in consequence, it was possible to correlate with that described by Pavlov as taking place in dogs. The observations themselves were made during an examination of 165 cases, which included examples of many of the usual types of digestive disorder and a number free from gastric symptoms. Fifty-three of the cases were treated with atropine.

The patients were prepared in the manner customary prior to a fractional gastric analysis, fasting for twelve hours before the test was begun. Total and free acidities were estimated by titration against decinormal caustic soda solution, using phenolphthalein and methyl orange respectively as indicators, and chlorides were determined by Volhard's method, all results being expressed as equivalent number of c.c. of decinormal caustic soda per 100 c.c. of gastric contents.

The Fasting Secretion.

If, after the small test-meal tube has been passed into the stomach and any resting contents withdrawn, it is allowed to remain in position but no gruel or other test medium given, a secretion of gastric juice usually follows. If this is drawn off at intervals of 10 minutes, each specimen will be found to measure from 5 to 50 c.c. according to the nature of the case. In the present series this occurred in about 60 per cent. of normal cases (whose secretion did not generally exceed 5 to 10 c.c. every 10 minutes), and in 80 to 90 per cent. of cases with symptoms of digestive disorder. The secretion may continue throughout the test, i.e. as long as 3 or 4 hours, or it may cease within the first hour. Galambos (2) describes a type of periodicity in the process, the quantity and concentration of the secretion becoming markedly reduced at the end of a half to one hour, which he regards as the first phase of exhaustion, lasting 10 to 15

[1] Received March 28, 1927.

minutes. After a second active interval of 30 to 60 minutes, a further period of exhaustion ensues, often lasting many hours. We have had several cases in which a free secretion occurred for about an hour, followed by a more or less sudden and permanent fall in quantity, and sometimes also in acidity, so that during the rest of the test only 1 or 2 c.c. of secretion were obtained at each aspiration; but we have not found a variation such as Galambos speaks of.

The character of the secretion varies from that of a clear colourless liquid of high acidity to that of a viscous mucus-containing fluid having no real acid value.

The error due to the patient swallowing saliva can be largely, though not entirely, avoided by his expectorating throughout the experiment. It is probable, nevertheless, that some saliva will still trickle down the outside of the tube, and pharyngeal or oesophageal secretion entering the stomach will also tend to obscure the true result. Further, it is impossible to keep the patient under strict supervision during the whole of the test to see that he carries out the instructions conscientiously.

The regurgitation of bile or other secretion from the duodenum is another source of complication. There is reason for believing, however, that if due precautions are taken in experiment and observation no gross error arises from these causes in the majority of cases. Exceptionally, error may occur in those cases with free salivary secretion or when the gastric secretion itself is small in amount.

The Effect of Atropine on the Gastric Secretion.

When investigating the effect of atropine, the drug was usually administered hypodermically:

(1) In order that its action might be more prolonged.

(2) To obtain clearer results, by thus avoiding the necessity of withdrawing unabsorbed drug from the stomach at the first aspiration, and by not introducing the drug dissolved in water into the stomach, water having been said to have a certain stimulating action on gastric secretion.

After doses of one-hundredth of a grain there followed a greater or less reduction of the fasting secretion in almost every case, normal or pathological. This was made evident by a fall in the acidity, or in the quantity of the secretion, or by both these effects (Charts 1 and 3). The variable nature of the result is probably due to the interaction of several more or less independent factors, and will be discussed after the question of chloride secretion has been dealt with. Moreover, the same type of response was not necessarily obtained on repeating the test.

To meet the possible criticism that the fall in secretion was due simply to the psychical effect of the act of injection, a preliminary injection of sterile water was given on one or two occasions. No fall in secretion occurred, but the customary effect was observed on a subsequent injection of atropine (Chart 1). A second injection of one-hundredth of a grain as the effect of the first dose was passing off appeared equally definite in its action.

When, instead of being administered subcutaneously, the drug was given by the mouth and twenty minutes allowed to elapse before aspiration was proceeded with, the same type of result was obtained, though the effect was of shorter duration, in part no doubt owing to the fact that the whole of the drug had not been absorbed in the allotted time.

It is possible to inhibit the secretion of acid completely in almost every case if larger doses of atropine are used, though it may be necessary to push the drug until minor symptoms of poisoning occur, such as dry mouth, tachycardia, and blurring of vision (3).

If, with the secretion thus inhibited, the patient is given gruel, still no secretion occurs (Chart 6). The tachycardia produced by these larger doses may be utilized to follow the rise and decline in the action of the drug. Thus, if a further injection is given at the point when the pulse-rate begins to fall again, the rate once more increases and the suppression of secretion is maintained (Chart 6). If, however, the second injection is delayed a little longer until free acid appears in the samples drawn off from the stomach, the atropine is no longer able to prevent secretion entirely, though the acid curve does not reach the same height under these conditions as in a control experiment without atropine (Chart 7).

It is necessary to remember that absence of acid in the samples does not of itself prove absence of acid secretion, as there are several neutralizing agencies which may intervene. The deduction of absence of secretion is more probably correct if, in addition, the total chlorides show no increase, since these include all hydrochloric acid secreted, whether neutralized subsequently or not. But if neutralization has occurred, the volume of the stomach contents will have been increased by the addition of the neutralizing fluid, and this dilution will have masked the increase in total chloride unless the neutralizing fluid itself contains chloride in a concentration not appreciably less than that of the fluid neutralized. The dilution of the meal given may be measured by including in it a small quantity of some substance which will remain unaffected throughout the test, which will exert no action on its own account, and which can be easily estimated. We have found creatinine useful for this purpose, after experiments which showed that it fulfilled the necessary conditions. The estimation of the creatinine in the various samples is then essentially an estimation of their gruel content when followed by the necessary mathematical treatment of the results. If no dilution has occurred it is obvious that there can have been no secretion.

If the patient whose fasting secretion has been completely inhibited by atropine, and who therefore fails to secrete after gruel, is given a caffeine solution (0·2 grm. in 100–300 c.c. of water), which he swallows, or which is poured into the stomach down the tube, a secretion of acid takes place in most cases, though it may be less in amount than in the control test with caffeine alone (Chart 8). Charts 5–8 represent tests carried out on one patient within the space of a few days, Chart 5 showing the results of an orthodox gruel meal. The other three charts have been commented on above.

A possible explanation of why caffeine is able to provoke a secretion of gastric juice when gruel fails to do so becomes evident if we accept the suggestion put forward by Hirschberg and Ganskau (4) that the fasting secretion corresponds to the psychical secretion of Pavlov, and is due, not to the presence of the tube in the stomach, but to the psychical stimulation occasioned by the unavoidable technique and conditions of the test. The more rigorous these conditions are made, the greater is the stimulus to secretion. The efferent fibres for this reflex effect are conveyed in the vagus, so that the secretion cannot occur when the vagal endings are paralysed by atropine or the nerves divided as in the experiments of Pavlov. But Pavlov found that even after section of the vagi a secretion occurred at the end of twenty minutes or longer after introducing meat into the stomach. This has been accounted for by the supposition that a hormone, gastrin, is liberated from certain cells of the gastric mucous membrane into the blood-stream, and is then capable of exciting the secretory cells, so that no intervention of a nervous mechanism is required. In a similar manner it seems reasonable to assume that caffeine on absorption is able to liberate this hormone or to stimulate the so-called 'chemical secretion' in some other way, whereas gruel does not. It must first undergo partial digestion by the psychical secretion, when some digestion product may be able to initiate the chemical secretion; but if for any reason no psychical secretion occurs with gruel, then no chemical secretion can occur (except possibly in the event of regurgitation of trypsin from the duodenum). A practical point thus arises, whether gruel is a suitable test-meal medium, more particularly in cases of apparent achlorhydria. Fear of the unknown nature of the impending proceedings may be sufficient to produce a temporary achlorhydria in a nervous patient, though on repeating the test in such cases a secretion of acid is usually obtained. At the same time, the fact must also be borne in mind that gruel, without the addition of salt (a necessary stipulation if chlorides are to be estimated), is a most unappetizing article of diet, so that it would not be surprising if it failed to arouse a psychical secretion when presented to the patient on a second occasion. Hence a verdict of achlorhydria, based on the findings of a gruel meal, may be misleading, and in such cases it might be advisable to test the effect of caffeine or bouillon in addition.

Katsch and Kalk (5) recommend a dilute solution of caffeine or of alcohol as a standard test medium, and point out the advantages for the subsequent chemical analysis of using such a clear, chemically simple, protein- and chlorine-free liquid. As far as research is concerned it is unfortunate that the effect of caffeine is not limited to that on gastric secretion, but that its other actions, such as heightened psychical activity and diuresis, may affect the secretion indirectly.

Pavlov and others state that water may excite the secretion of gastric juice, and Bergheim, Rehfuss, and Hawk (6) suggest the use of water in place of gruel as a test fluid. Since the water of gruel fails to arouse a secretion in a patient whose fasting secretion has been stopped by atropine, it would appear probable that it is the psychical secretion, or at least a secretion for which the integrity of the vagus is necessary, that is produced when water is the stimulant.

When the stomach has emptied of the test-meal, an 'after-secretion' is frequently obtained and may be withdrawn in the same manner as the fasting secretion (5). Atropine is effective in inhibiting this 'after-secretion' (Chart 2), which fact at first sight appears to contradict the opinion already advanced, since it is supposed to be the chemical secretion alone which occurs towards the end of a meal. But under the conditions of experiment, the after-secretion of the test-meal may be regarded as almost identical with the fasting secretion of the approaching dinner, so that the contradiction is more apparent than real.

When the dosage of atropine was kept within pharmacopoeial limits, the degree of inhibition of secretion was found to vary widely in the different cases. In one or two no definite effect could be detected; in others there was a complete cessation of secretion, which continued to the end of the experiment, i. e. as long as three hours; the remaining cases showed results between these two extremes. But if the foregoing interpretation of gastric secretion is correct, one might expect that the greatest fasting secretion would occur in cases of reflex dyspepsia, and this, in general, seemed to be the case, more particularly when associated with duodenal ulcer or appendicular disease. Moreover, it is in these conditions that atropine is likely to produce its most beneficial effects, since it was found to lead to a greater absolute, though not necessarily a greater relative, diminution in the amount of gastric juice secreted.

In an earlier communication (1) the effect on the acidity of the gastric contents of administration of atropine and belladonna was described, and it was concluded that the diminution in acidity found was a result of increased or more frequent duodenal regurgitation and possibly, too, of a lessened secretion of gastric juice. The present investigation has thus confirmed the latter factor and has emphasized the large part played by the nervous element in gastric secretion during a gruel meal.

As also mentioned in the previous paper, there is no doubt that atropine increases the emptying rate of the stomach. But when the drug is given until minor toxic symptoms appear and the fasting secretion is stopped, the emptying of the stomach is delayed (cp. Charts 5, 6, and 7).

It has been described already how the tachycardia produced by the larger doses of atropine is useful as an index of the rise and fall in the action of the drug. When only pharmacopoeial doses were used no alteration in the pulse-rate could be detected as a rule, so that the effect of atropine on the vagus is shown earlier by its gastric than by its cardiac manifestations.

The Fasting Secretion in Achlorhydria.

The character of the fasting secretion occurring in achlorhydria varied according to the cause of the condition. In cases where the achlorhydria was of psychical origin, the secretion was small in quantity and contained a high proportion of mucus. There was little secretion, too, in those cases of carcinoma of the stomach showing achlorhydria, but when lactic acid or other abnormal con-

stituents were present the volume of fluid withdrawn was greater. Cases of pernicious anaemia examined usually showed a true achylia, but in one case a secretion of fluid containing 0·35 per cent. of sodium chloride occurred, which appeared to be unaffected by the administration of one-hundredth of a grain of atropine.

Rioch and Cameron (7) did not find any secretion of chloride in pernicious anaemia, but since the test-meal which they used itself contained 0·16 per cent. of chloride they would be unable to detect a secretion with a concentration of less than 0·16 per cent. unless they measured also the dilution of the meal, which they do not appear to have done.

The Chlorides of Gastric Juice.

In most of the cases studied the total chloride content of the various specimens was estimated, the inorganic chlorides being taken as the difference between the total chlorides and the total acidity, experience having proved that this is sufficiently accurate in the absence of organic acids.

It is impossible to put forward anything more than a tentative explanation of the results obtained, owing to the number of uncontrollable factors present and to the lack of definite knowledge of the actual existence, neutralizing power, and chloride content of the hypothetical alkaline pyloric secretion, and of the possible occurrence of duodenal regurgitation unaccompanied by bile. There is great diversity of opinion on this latter point, some writers taking it as an established fact, others considering that the possibility may be ignored. It is quite conceivable that it is more likely to occur during a fasting secretion test than in the course of a gruel meal, for the digestive process will supply a greater stimulus to the outflow of bile into the duodenum than the mere presence of the tube in the stomach. Work is in progress at present in this laboratory which it is hoped will decide the question.

A careful analysis of all the curves of fasting secretion, omitting those sections influenced by the appearance of bile, revealed three types of relative variation between the total chlorides and the acidity:

(1) The two curves run more or less parallel.

(2) The total chlorides show little or no change, whilst the acidity undergoes quite definite fluctuations. This occurs most frequently when the patient is under the influence of atropine.

(3) The curves follow an apparently haphazard and independent course. This, however, is unusual except in cases with bile present.

All these variations are illustrated by Chart 3, the curves running in an approximately parallel fashion until the action of the atropine sets in, when the variation changes to the second type. The third type is seen when the action of the atropine has passed off. This chart, which shows the atropine effect quite clearly, is worth discussing in greater detail. It is improbable that the fall in acidity after the atropine injection is the result of neutralization by regurgitation

from the duodenum, since, apart from the questionable significance of the non-appearance of bile, there is a smaller quantity of fluid obtained, whereas neutralization would have led to a rise in quantity owing to the added volume of the neutralizing fluid (as seen in Chart 1, samples 8 and 9). This last point also

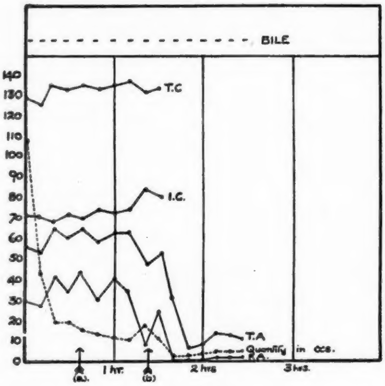

Chart 1.

Patient A. Fasting secretion only.
Arrow (a) = hypodermic injection ♏ v sterile water.
,, (b) = hypodermic injection gr. $\frac{1}{100}$ atropine sulph.

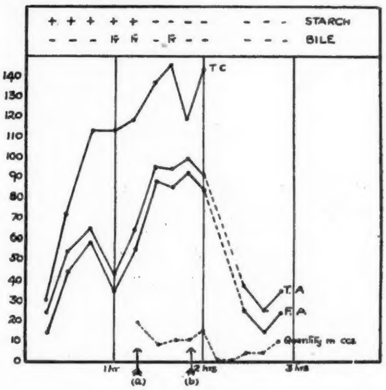

Chart 2.

Patient B. Gruel meal and 'after-secretion'.
Arrow (a) = all gastric contents withdrawn.
,, (b) = hypodermic injection gr. $\frac{1}{100}$ atropine sulph.

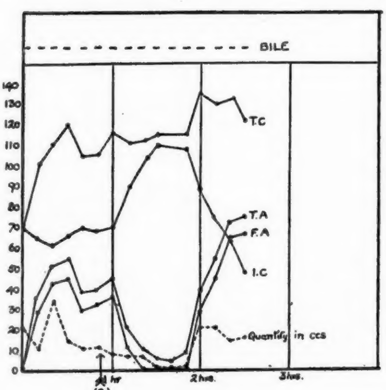

Chart 3.

Patient C. Fasting secretion only.
Arrow (a) = hypodermic injection gr. $\frac{1}{100}$ atropine sulph.

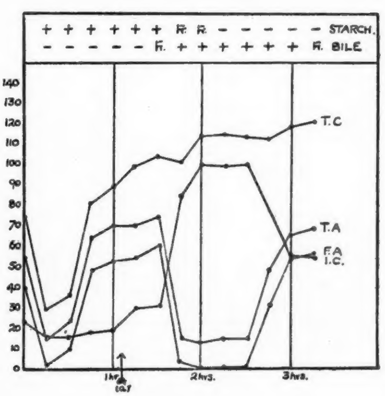

Chart 4.

Patient D. Gruel meal.
Arrow (a) = ♏ x tinct. belladonnae in water given by mouth.

argues against neutralization by saliva or mucus, as do the following:

(1) The specimens did not show any apparent increase in mucus content.

(2) Examination has demonstrated that mucus and saliva contain very little alkali, most of the acid required for titration (using methyl orange as indicator) becoming combined with the protein. Thus their effect as acid neutralizers would

be shown by a fall in the free acidity without a corresponding fall in the total acidity. In the case under discussion the two curves fall together.

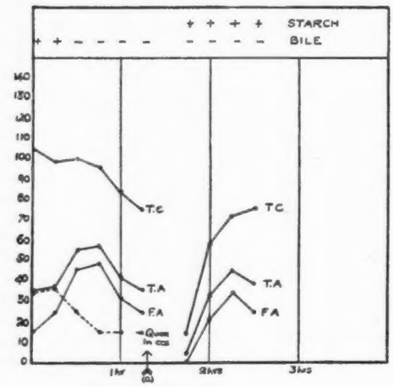

CHART 5.

Patient E. Fasting secretion and gruel meal.
Arrow (*a*) = gruel.

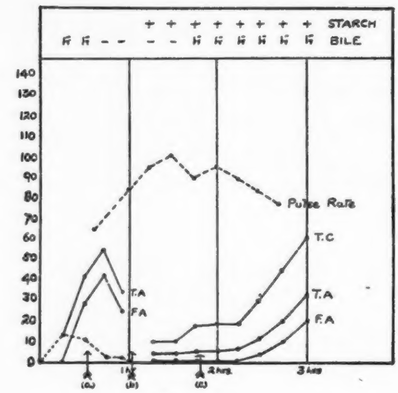

CHART 6.

Patient E. Fasting secretion and gruel meal.
Arrow (*a*) = hypodermic injection gr. $\frac{1}{50}$ atropine sulph.
„ (*b*) = gruel.
„ (*c*) = hypodermic injection gr. $\frac{1}{100}$ atropine sulph.

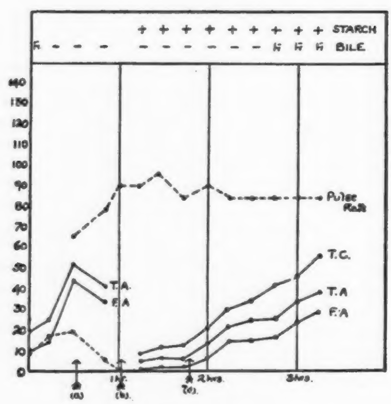

CHART 7.

Patient E. Fasting secretion and gruel meal.
Arrow (*a*) = hypodermic injection gr. $\frac{1}{50}$ atropine sulph.
„ (*b*) = gruel.
„ (*c*) = hypodermic injection gr. $\frac{1}{50}$ atropine sulph.

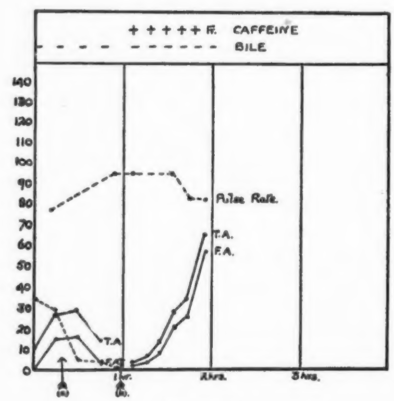

CHART 8.

Patient E. Fasting secretion and caffeine.
Arrow (*a*) = hypodermic injection gr. $\frac{1}{50}$ atropine sulph.
„ (*b*) = 0·2 grm. caffeine in 200 c.c. water.

(3) Mucus and saliva have a low chloride content. This would necessitate a distinct drop in the total chloride curve. No such drop occurs.

If then neutralization may be excluded, the secretion of acid must have diminished, but decrease in quantity alone would have left the acidity and

chloride values unchanged. It is necessary to suppose that, in addition, the chloride ion no longer secreted as hydrochloric acid was secreted instead as inorganic chloride (i. e. as sodium or other mineral chloride), or, to carry the idea a stage farther, that a secretion of chloride already occurring along with the acid

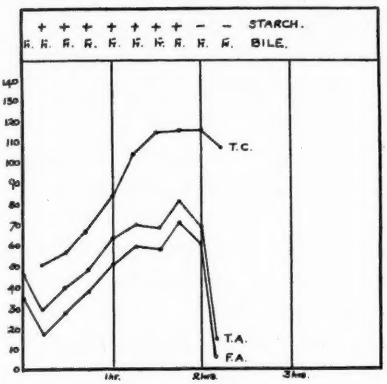

CHART 9.
Patient F. Gruel meal.

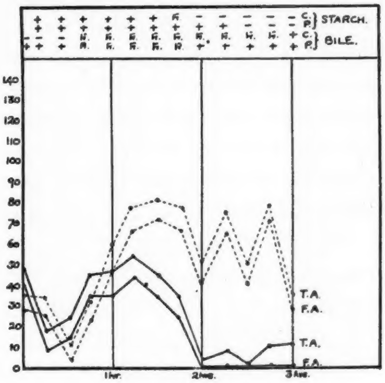

CHART 10.
Patient F. Gruel meal, with two tubes.
Dotted lines = cardiac tube.
Full „ = pyloric tube.

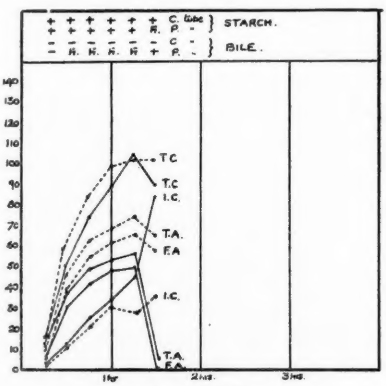

CHART 11.
Patient G. Gruel meal, with two tubes.
Dotted lines = cardiac tube.
Full „ = pyloric tube.

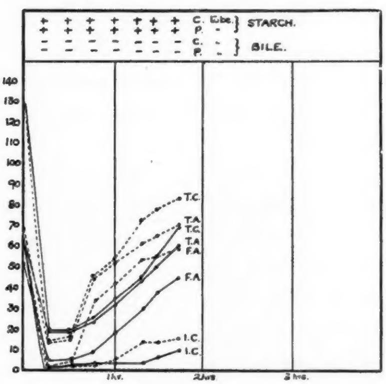

CHART 12.
Patient H. Gruel meal, with two tubes.
Dotted lines = cardiac tube.
Full „ = pyloric tube.

secretion was increased in concentration proportionately to the fall in concentration of acid. The latter suggestion implies a chloride secretion independent of that of acid, which may, however, appear to show varying degrees of dependence by the superimposition of the alternative secretion of chloride for acid or vice versa. When the total chloride and acidity curves run parallel it is then only necessary to assume that chloride is being secreted at constant concentration, whilst the concentration of acid varies (seen in Charts 1 and 3).

Katsch and Kalk (8), reasoning on different grounds from a series of curves obtained by the alcohol test, also conclude that there is a secretion of chloride independent of that of acid. The hypothesis applies, of course, at all times, whether the subject is under the influence of atropine or not. Such a chloride secretion may largely account for the fact that in a gruel meal the total chloride and acidity curves tend to diverge more and more as the meal progresses. The total chloride curve may thus still be regarded as giving the truest index of gastric secretion, though not quite in the sense in which the idea was first advanced by Bolton and Goodhart (9, 10).

In describing the effect of one-hundredth of a grain of atropine on the fasting secretion it was stated that a diminished secretion was the usual result. The actual effects seen were as follows:

(1) A diminution in the quantity of secretion, the acidity and chlorides remaining practically constant. This is explained on the assumption that the chloride and acid secretions were depressed to the same relative degree.

(2) A rise in quantity with a fall in acidity. This occurred in only a few instances, and was accompanied by the appearance of bile, which would account for the increase in quantity, and would imply neutralization as part cause of the fall in acidity.

(3) A fall in acidity, whilst quantity and total chlorides remain approximately constant. This may be explained by a greater influence of the atropine on the acid than on the chloride secretion, as described above with Chart 3. It is seen on comparing samples Nos. 7, 8, and 9 on this chart.

(4) A fall in quantity and acidity with more or less constant total chloride. This suggests a depression of both secretions, the greater effect being produced on the acid.

In an endeavour to interpret curves of fasting or after-secretion and those of a test-meal there is one point which is liable to be overlooked. In the former case, the specimens obtained are independent of one another in the sense that the stomach is completely emptied (supposedly) at each aspiration. In a test-meal, on the other hand, only a sample of the stomach contents is withdrawn, the remainder serving as a residue of unknown volume into which the subsequent secretions of unknown compositions are poured, so that the composition of the succeeding sample is largely influenced by that of its predecessor and by the rate at which the stomach is emptying. One result of this distinction is manifested by a comparison of Charts 3 and 4. Apart from the different relative levels of the inorganic chloride curves, the general form of the two charts is strikingly similar. The former, as already explained, shows the effect of atropine in diminishing secretion. The latter is of a gruel meal and illustrates the action of atropine in causing duodenal regurgitation and neutralization, as shown by the abrupt fall in the acid curve and the corresponding rise in that of inorganic chloride, with the simultaneous appearance of bile. A simple effect of atropine on the secretion of acid and chloride is inadequate to explain this type of curve when it occurs in the course of a gruel meal.

The Incomplete Mixing of the Gastric Contents.

The interpretation of a gruel meal chart is, on the whole, simpler than that of one of fasting secretion, for minor sources of error, such as swallowed saliva, in most cases may be ignored; but even here puzzling relative variations in the total chloride and acidity curves often occur, e. g. a fall in the former with a simultaneous rise in the latter, the variation being greater than can be accounted for by changes in secretion. This is most simply explained on the assumption that mixing of the stomach contents has been incomplete, and there is good reason for thinking that such may actually be the case. Any one who has performed a number of test meals must have noticed that on his withdrawing a sample the first portion is sometimes visibly of a different nature from that obtained later. In several of such cases we have collected and analysed the two parts separately. The following were some of the results obtained:

		Free Acid.	Total Acidity.	Total Chlorides.	Inorganic Chlorides.
Case A.	1st portion	27	41	59	20
	2nd ,,	54	65	90	25
Case B.	1st portion	45	56	109	56
	2nd ,,	23	33	112	83
Case C.	1st portion	nil.	4	115	111
	2nd ,,	24	38	119	82
Case D.	1st portion	6	23	127	108
	2nd ,,	80	92	138	51

In other cases we have changed the position of the patient and taken a second sample (A and B below), or have raised the tube in stages and taken samples at the different levels (C and D below).

		Free Acid.	Total Acidity.	Total Chlorides.	Inorganic Chlorides.
Case A.	1st portion	70	81	109	29
	2nd ,,	nil	10	111	102
Case B.	1st portion	63	73	101	28
	2nd ,,	42	43	120	77
Case C.	1st portion	6	15	108	95
	2nd ,,	48	57	115	60
	3rd ,,	63	73	123	55
Case D.	1st portion	1	9	117	108
	2nd ,,	55	63	127	67
	3rd ,,	80	90	129	40
	4th ,,	90	106	134	30

In order to demonstrate incomplete mixing more conclusively, several patients have swallowed two tubes fastened together, so that when the lower one was situated near to and on the proximal side of the pylorus, the upper one would be at the cardiac end of the stomach. To confirm the fact that the pyloric tube did not pass into the duodenum (though only twenty-four inches of tube were swallowed), the patient was examined by the X-rays on one occasion at the

beginning and the end of the test. Samples were withdrawn from the two tubes simultaneously. Chart 9 is the average of two gruel meals carried out in one case, and Chart 10 a third test on the same patient using two tubes—dotted lines representing the results obtained from the cardiac tube, full lines those from the pyloric tube. Chlorides have been omitted in Chart 10 to avoid confusion. The great divergence in this case seems to be the result of a tendency towards hyper-acidity, together with a free duodenal regurgitation, the latter producing a pronounced effect on the composition of the fluid in the neighbourhood of the pylorus. Charts 11 and 12 are from other cases and illustrate the more usual degree of variation found, viz. up to 0·07 per cent. hydrochloric acid between the two ends of the stomach. It is noteworthy that it is almost invariably the pyloric sample that shows the lower value. In Chart 11 this seems to be largely due to neutralization, as the pyloric total chloride curve is not far below that of the cardiac tube, whilst bile is present in the pyloric samples. In Chart 12 the reason is apparently that less secretion has been added to the pyloric portion, as shown by again comparing the relative levels of the total chloride curves. Since the difference of acidity between the contents of the cardiac and pyloric ends of the stomach does not usually exceed 0·07 per cent., the results obtained by fractional gastric analysis in routine clinical work are not invalidated thereby, but the discrepancy may be of importance in more exact determinations of secretory changes such as those discussed in the present paper, where deductions have therefore been drawn with due caution and only after numerous observations.

Summary.

1. The occurrence and characters of the fasting gastric secretion are described.

2. The effect of gr. $\frac{1}{100}$ atropine sulphate is to depress this secretion in greater or less degree.

3. Larger doses (gr. $\frac{1}{50}$–$\frac{1}{25}$) inhibit the secretion completely by paralysing the vagal endings. Gruel then fails to stimulate any secretion, but caffeine is still able to do so.

4. The probable identity of the fasting secretion with the 'psychical secretion' of Pavlov is pointed out. Secretion occurring whilst the fasting secretion is inhibited probably corresponds to the 'chemical secretion'.

5. The most copious fasting secretion occurs in cases of reflex dyspepsia associated with duodenal ulcer or appendicular disease.

6. Atropine is effective in inhibiting the 'after-secretion' occurring when the stomach has emptied of the test-meal.

7. The diminution in gastric acidity after atropine is due to:

(*a*) its inhibitory effect on the fasting secretion.

(*b*) its facilitating duodenal regurgitation, with consequent neutralization of acid.

In its usual dosage it hastens the emptying of the stomach; in larger doses it retards it.

8. Decrease of secretion may be observed after doses too small to cause acceleration of the pulse.

9. The fasting secretion in achlorhydria is described.

10. The relation between the chloride and acidity curves in fasting secretion observations and in test-meals is discussed, and arguments adduced in favour of a chloride secretion independent of that of acid.

11. Evidence of incomplete mixing of the stomach contents is advanced, a difference up to 0·07 per cent. acidity between the cardiac and pyloric ends of the stomach being usual, whilst a much greater divergence may occur on occasion.

In conclusion, I wish to thank Professor Craven Moore and Professor Raper for their valuable criticisms during the progress of the work, Dr. Twining and Mr. Bromley for the X-ray examination, the members of the Honorary Staff of the hospital for permission to make use of their patients for this investigation, and the Nursing Staff for their willing co-operation.

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THE COURSE AND TREATMENT OF AURICULAR FLUTTER[1]

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With Plate 1

AURICULAR flutter may be as important a determining factor in heart failure as auricular fibrillation, but it is not so common nor so easily diagnosed without cardiographic methods. Flutter in paroxysms constitutes a special variety of paroxysmal tachycardia. Since Ritchie's monograph (41) was published in 1914, the physiology of flutter has been elucidated by Lewis and others, and quinidine has been introduced into therapeutics.

We have observed 52 patients with flutter between the years 1913 and 1926, of whom two only were seen during the War (1914–19). From an analysis of these and from reference to the literature since 1914, we have summarized the associations and clinical course of flutter. Special attention has been given to the after-histories and to the ultimate results of treatment by digitalis or quinidine.

Clinical Features.

Paroxysmal and established flutter. Much prominence has been accorded the paroxysmal variety of flutter, though it is more often an established condition when first diagnosed. Considering it as established whenever it failed to end spontaneously within fourteen days, then of our 52 cases 40 had established, and 12 paroxysmal flutter only. In only 5 of the established cases did the history suggest previous paroxysms. A history of previous attacks of palpitation in these patients does not always signify paroxysms of flutter, for attacks of palpitation are common in the course of established flutter from a sudden increase in the ventricular rate; for instance, 4 : 1 changing to 2 : 1 block, or 2 : 1 changing to 1 : 1 rhythm. Thus Case XI with continuous flutter complained of bouts of palpitation starting and ceasing abruptly; in one of them an electrocardiogram (EC.) was obtained which showed flutter with a 1 : 1 rhythm, rate 254 (Fig. 5). A few minutes later he announced that the attack was over, and the EC. then

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[2] Working under the Paterson Bequest.

showed flutter with a 2:1 response of the ventricles (A. 254, V. 127, Fig. 5). In the majority of the established cases flutter had probably existed for several months or longer when first seen. The tendency of established flutter to change to fibrillation spontaneously is slight, for this occurred only twice.

Paroxysmal flutter, in contrast, frequently alternates with fibrillation; in 7 of our 12 paroxysmal cases periods of fibrillation were actually recorded. Except when they are merely terminal or only begin within a few months of death, the paroxysms almost always recur and often become more frequent. Exceptions were Case XXII, who had an interval of two years' freedom from paroxysms, though they returned before death, and Case IV, who died probably in flutter, after remaining free for four years. Case VIII has had repeated paroxysms for four years at intervals of a few months, and Case XXXVI, whose attacks began eight years ago, still has them about once a week. The duration of individual paroxysms is usually less than a day, but may be as long as ten days. Instances have been reported in the literature of paroxysms of flutter occurring over prolonged periods. Two of Mackenzie's (30) patients had attacks for 35 and 36 years respectively, and two described by Lewis (26) for 30 and 38 years.

Thus in about 25 per cent. of cases flutter is purely paroxysmal and is then frequently associated with paroxysms of fibrillation. Once a paroxysm has occurred, recurrences are almost certain. Paroxysmal flutter is far less common than paroxysmal fibrillation. In the remaining 75 per cent. of cases flutter is an established condition when first observed, and is unlikely to disappear or to change to fibrillation apart from therapeutic measures.

General symptoms. Heart failure of the congestive type was present at the time of initial observation in 24 of our 52 cases. In the remainder gross heart failure was absent, although some of them subsequently died with failure. Generally speaking, the symptoms were those of a degree of heart failure with the special symptoms of tachycardia added. Thus breathlessness, palpitation, giddiness, general weakness, with faintness and disinclination for effort, were common. Thoracic pain was not uncommon, occurring in twelve patients apart from those considered to have angina pectoris. It was usually referred to the left breast, but occasionally it was sternal or epigastric. Such pain may arise with the onset of a paroxysm, or follow exertion in continuous flutter; in three cases it was accompanied by numbness of the left arm. It is important to realize that paroxysmal flutter may cause a severe pain in the chest, and that sometimes this closely simulates angina. On the other hand, a sufferer from coronary angina pectoris may get flutter either as a result of coronary thrombosis or apart from it. If flutter persists in such cases, Mackenzie's experience was that heart failure replaced the anginal symptoms, and this happened in our Case XLIX. In Case XXIV, however, we witnessed several typical attacks of angina during continuous flutter. The patient had suffered for eight years from sternal pain radiating to the arms, induced by exertion and causing him to stop if walking.

Syncope. Syncope during flutter is undoubtedly less common than some

have assumed, for it occurred in only five of our cases. The patient may fall and injure himself, or rarely may become deeply comatose, as described by Mackenzie (32) and Blackford and Willius (6). The attacks often follow exertion, and are probably always due to the assumption by the ventricles of the full auricular rate. We know of only one record obtained during actual syncope (Theodore Thompson (30)), and in that the radial pulse almost disappeared, but faint waves indicated a 1 : 1 ventricular response. The fact that both syncope and 1 : 1 rhythm are often induced by effort points to an association of these two events. A paroxysm of 1 : 1 rhythm, however, does not always cause syncope, for two of our patients, Cases XLV and XI, actually attended the out-patient department during 1 : 1 flutter with recorded ventricular rates of 275 and 254 respectively.

The pulse. The pulse, when first recorded, was regular in 30 and irregular in 22 of our 52 cases. In eight of the regular cases an occasional irregularity was noticed, while six of the irregular cases had some periods of regularity. In 36 cases the initial pulse-rate lay between 120 and 170, in 10 between 90 and 120 per minute. In four cases the pulse was unusually slow, apart from treatment, the rates being 64, 45, 42, and 35 respectively. In the remaining two cases the initial pulse-rates were 254 and 275, 1 : 1 flutter being present when they were first seen. Generally speaking the pulse was irregular when below 130, and regular at or above this rate. Where the pulse was rapid and regular, pulsus alternans was common. An irregularity rather characteristic of flutter is bigeminy at a relatively rapid rate, due to alternating 2 : 1 and 4 : 1, or 2 : 1 and 3 : 1 *a.-v.* block ; the latter simulates pulsus alternans (Fig. 1).

During Cheyne-Stokes breathing the degree of block may differ in the apnoeic and hyperpnoeic phases, or alternation may become exaggerated during the hyperpnoea. Fig. 2 shows a tracing of radial pulse and respiration taken during Cheyne-Stokes breathing and flutter in Case XLI, which illustrates the change from a regular pulse during apnoea to an irregular pulse during hyperpnoea. Similar records have been shown to us by Dr. A. J. Whiting.

Blood-pressure. We have not observed unusually low blood-pressure during flutter. In fourteen cases in which we observed the effect on the blood-pressure of a change from flutter to normal rhythm we found the systolic pressure raised by 10 m.m. or more in eight, and unaltered or slightly lowered in six. The diastolic pressure, where it could be recorded in flutter, was often high relative to the systolic, and the pulse pressure consequently small. In those cases the diastolic pressure fell with the onset of normal rhythm, and the pulse pressure increased, as seen in the figures below.

Case.	Blood-pressure in Flutter.	Blood-pressure in Normal Rhythm.
XVII	190/90	205/80
XXXVIII	150/110	140/65
XIX	200/150	215/115
XVIII	140/125	135/100
L	110/85	120/75 (nodal rhythm)
LI	125/95	125/75
	152/109	157/85

In Case XXI the following observations were made during digitalis treatment:

Average of 11 readings in 2 : 1 flutter, 119/90.

Average of 5 readings in 4 : 1 flutter, 131/77.

Average of 8 readings in fibrillation, 132/–.

Embolism. Nine of our cases had embolism, though of those actually under observation when it occurred none happened to be in flutter. In six flutter was established, in three paroxysmal; four had mitral stenosis. Of those with established flutter, Case XXIX had popliteal embolism a month before she was seen in flutter, which was probably present at the time. One had cerebral embolism during fibrillation, seventeen months after the abolition of flutter. Two had pulmonary infarction shortly after the onset of normal rhythm. The remaining two cases had cerebral embolism; in one hemiplegia occurred eight days after the change from flutter to normal rhythm, and in the other it coincided with the change from fibrillation to normal rhythm, after digitalis. Embolism after the change to normal rhythm has been reported by Lewis (26) and by Mackenzie (31). Turretini (48) has recorded an instance of embolism during flutter in a case of mitral stenosis, but he regarded the valvular lesion responsible. There seems to be less danger of embolism during established flutter than during established fibrillation. Of the three cases with paroxysmal flutter, embolism occurred during fibrillation in one, and followed long paroxysms of flutter in two. Case VIII, with mitral stenosis and aortic incompetence, had had embolism of the right arm and leg before we saw her. Two years later a further embolism of the right leg and a cerebral embolism followed a paroxysm of flutter lasting over a week. Case XXXVI developed hemiplegia the day after the cessation of a paroxysm which had lasted ten days. Intra-auricular thrombi may be formed during long paroxysms of flutter and then be expelled on the return of normal auricular activity.

The Effects of Vagal Pressure.

It is well known that pressure on the vagus in the neck or ocular compression during flutter may induce slowing or even standstill of the ventricles without appreciably affecting the auricles. How often this effect is obtainable apart from digitalis is difficult to estimate, as published records often omit to say whether digitalis was being given or not. Pardee (36) states that vagal pressure never fails to slow the ventricles, and Volle (51) obtained positive results in 15 out of 20 cases. In 12 undigitalized cases in which we tried vagal pressure the ventricles were unaffected in 10. In Case XI no effect was recorded even during 1 : 1 flutter. In several cases vagal pressure after digitalization gave rise to considerable ventricular slowing where such pressure had previously been ineffective. The procedure is not always devoid of risk, for 'artificial Stokes-Adams syndrome' may be produced (19). It is not only in flutter, however, that vagal stimulation slows the pulse; a similar effect may be produced in a proportion of patients with normal rhythm, or with fibrillation or even with paroxysmal

tachycardia (Gallavardin (14)). In Cases XV and XLVI vagal stimulation was equally effective in slowing the ventricles during both flutter and normal rhythm, and once this led us to assume erroneously the presence of flutter. We conclude that pressure on the vagus in the neck is usually effective in producing ventricular slowing in cases of flutter under the influence of digitalis, but apart from this its effects are inconstant and of little diagnostic value.

Aetiology and Clinical Varieties.

Wedd (53) found 9 cases of flutter and 137 of fibrillation in 1,200 patients examined by electrocardiograph; and Blackford and Willius (6) in 3,500 patients similarly examined found 16 of flutter to 363 of fibrillation. These statistics suggest that the ratio of the frequency of flutter to that of fibrillation is about 1 to 20. In our 52 cases the average age when first observed in flutter was 48, the youngest patient being 12 and the oldest 76 years. Forty-four were males and eight females. The following table shows the age incidence:

1 in 15
1 in 24

10-19 years.	20-29 years.	30-39 years.	40-49 years.	50-59 years.	60-69 years.	Over 70 years.
4	3	6	14	10	13	2

Thus 75 per cent. were over 40, and the maximum incidence happened to be between 40 and 70 years. The conditions with which flutter was associated in our cases were as follows:

Chronic rheumatic heart disease, 14; cardiac enlargement (excluding high blood-pressure and syphilis), 14; high blood-pressure and chronic nephritis, 6; infections (including syphilis), 5; heart otherwise normal, 5; coronary thrombosis, 3; acute rheumatism, 2; hyperthyroidism, 2; congenital heart disease, 1.

Flutter in otherwise healthy hearts. In the absence of cardiac enlargement, valvular disease, arteriosclerosis, or raised blood-pressure, and where syphilis and rheumatism can be excluded, even the presence of a disorder of function such as auricular flutter does not justify the clinical assumption that any lesion such as 'myocarditis' is the underlying basis. In the five cases included here there was no evidence of heart disease, apart from flutter.

Case XI Quinidine Series A

Dr Moir *Case XXXVI.* Male, 67. First seen May, 1920. No rheumatism or syphilis. Always well until 1918, when attacks of palpitation began. Since then attacks have occurred almost weekly, the longest lasting a few days. EC. during attack showed flutter, A. 302, V. 151. In another attack EC. showed fibrillation. In April, 1926, at 73 years of age, he could still walk 20 miles in hilly country. No abnormal signs ever found in heart or vessels. Between attack EC. is physiological. Dec 1927 Coronary thrombosis T3 inverted

Case XXXV. Male, 18. No rheumatism or syphilis. Well until 1921, when, after 'influenza', his pulse became rapid and irregular. After three months' rest in bed he did not improve, and polygrams then showed flutter. Digitalis and quinidine were given and an EC. proved the return of normal rhythm. Heart normal in size. No murmurs. B.P. 120/75. Four years later he was in good health and able to play football.

Case XXXVIII. Male, 65. Well, except for symptoms of enlarged prostate, until March, 1921. After a cystostomy, dyspnoea, cyanosis, and signs of heart failure appeared. Pulse regular, 160 a minute. Polygrams showed flutter. Heart clinically normal. B.P. 150/110. Digitalis was given and prostatectomy completed during flutter. Further digitalis then restored normal rhythm, confirmed by EC. He regained normal health and remained well until 1926, when he died from pelvic neoplasm. No heart symptoms preceded his death.

Case XXXIV. Male, 52. No rheumatism or syphilis. Well until October, 1922, when tachycardia began during 'influenza'. Dyspnoea; pulse rapid and uncountable. Heart clinically normal. Arteries normal. B.P. 110 systolic. EC. showed flutter, A. 322, V. 161. After 16 days of flutter, quinidine restored normal rhythm. Frequent recurrences of flutter since, always cut short by quinidine. Otherwise three years after the onset of flutter, still in good health and able to work.

Case XXXVII. Male, 33. Seen in February, 1923, complaining of dyspnoea, giddiness, and pain under the left breast. No rheumatism or syphilis. W.R. negative. Heart normal in size (X-ray). No murmurs. B.P. 150 systolic. Pulse infrequent, 40–50, and irregular. Polygrams, flutter, A. 245, V. 45. Digitalis abolished flutter, but EC. then showed nodal rhythm. Two years later EC. showed fibrillation. Quinidine caused nodal rhythm to return, but fibrillation soon recurred and has persisted. In 1926, seven years after first seen in flutter, he was in good health and at work. Heart clinically normal; EC. fibrillation.

Case XXXV, after the restoration of normal rhythm, not only regained normal health but was able to enjoy any degree of physical exertion. Yet during flutter he had been entirely incapacitated, and after three months' rest in bed was unimproved. Case XXXVIII had never experienced cardiac symptoms until the severe degree of failure which resulted from a week of flutter. He was well five years later and had no return of cardiac symptoms. The common feature in this group was the considerable degree of disability during flutter and the normal functional capacity during sinus rhythm.

Flutter in acute rheumatism. Of the disorders of rhythm encountered in the course of rheumatic fever and acute carditis, auricular flutter is probably the least frequent, for the literature contains records of only eight such cases (8, 34, 35, 37, 44, 47). Cohn and Swift, in 2,591 electrocardiograms from 37 cases, found flutter only once. In two of our series flutter was recorded during acute rheumatic infection.

Case XXXIX. Female, 19. Admitted to hospital in November, 1920, with fever and arthritis. Heart enlarged; mitral stenosis and aortic incompetence. Frequent paroxysms of flutter were recorded by polygrams, and later flutter became continuous, and was recorded by EC., A. 350, V. 165. After 13 drachms of tincture of digitalis in 10 days an EC. showed normal rhythm with auricular extra-systoles. Normal rhythm persisted. In September, 1924, she returned to hospital with acute carditis and heart failure, and died in 12 days. Polygrams before death showed normal rhythm.

Case XL. Male, 15. Previous rheumatic fever aged eight. Admitted to hospital in February, 1922, four weeks after the onset of his second attack, with fever and signs of pericardial effusion. Polygrams showed flutter, confirmed by EC. After digitalis had failed, quinidine restored normal rhythm (EC.). Signs of

aortic incompetence were now obvious. Subsequent records have all shown normal rhythm, and in January, 1926, he was in good health, working as a clerk.

Flutter in other infections, including syphilis. We are unable to find in the numerous studies of heart rhythm in diphtheria any proved case of flutter. Cases in which polygrams were inconclusive but suggestive are recorded by Hume (21), Schwensen (45), and Bie and Schwensen (4). Hart (18) obtained an EC. of flutter during lobar pneumonia, and Wedd (53) during infective endocarditis. Apart from the two cases of acute rheumatism, three of our patients had flutter during acute febrile illnesses.

Case XLII. Infective endocarditis. Male, 34. First seen October, 1922. Heart enlarged and systolic apical murmur. Pulse regular, rate normal. Liver enlarged; no oedema. Blood and casts in urine. Fingers clubbed. In November, 1922, violent palpitation began suddenly; pulse regular, rate 143. Pericardial friction, followed by effusion and severe heart failure. Polygrams conclusive of flutter. Digitalis induced fibrillation, followed by normal rhythm, which persisted until death two weeks later.

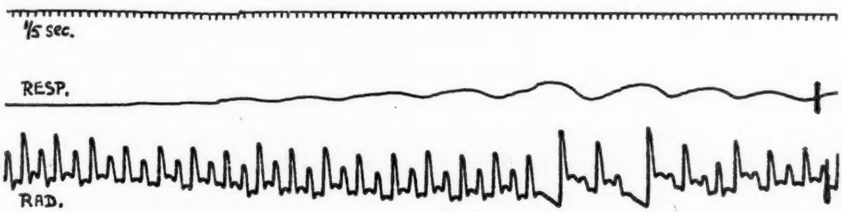

FIG. 2. Respiration and pulse showing Cheyne-Stokes breathing with flutter. Pulse regular and alternating, rate 135, during apnoea; irregular during hyperpnoea. (Case XLI.)

Necropsy. Fibrinous pericarditis with effusion. Infective endocarditis of sclerosed mitral valve. Infarction of spleen and right kidney. Chronic inflammatory nephritis. The auricular muscle showed microscopically a slight degree of fibrosis, without cellular infiltration.

Case XLI. Empyema and septicaemia. Male, 32. In March, 1922, bronchitis and jaundice with some heart failure, followed by pulmonary infarction. Fever persisted and rib resection was performed for empyema. Shortly afterwards the pulse became rapid and irregular with periods of regularity, rate 135, and alternation. Polygrams showed flutter. In spite of quinidine and digitalis flutter persisted. Jaundice, purpura, and femoral thrombosis developed, and he died in August, 1922. No necropsy.

Case XLIII. Pulmonary tuberculosis; arteriosclerosis. Male, 56. Seen in May, 1916, complaining of breathlessness, cough, wasting, palpitation, and giddiness. W.R. negative. There was fever and wasting. Crepitations at left apex. Sputum contained T.B. Pulse regular, rate 160, sometimes irregular. Heart enlarged, no murmurs. EC. flutter, A. 320, V. 160. Digitalis induced fibrillation, then normal rhythm. He improved temporarily, but died in two months from tuberculosis. There was one recurrence of flutter before death.

Syphilis is not a common cause of auricular fibrillation or of flutter, and heart failure in uncomplicated cardiac syphilis usually occurs with normal rhythm (39). Cowan and Ritchie (9) state that evidence of antecedent syphilis

is found in 10 per cent. of cases of flutter; we do not interpret this as implying that these 10 per cent. had cardiac syphilis. A positive Wassermann reaction does not exclude arteriosclerosis or high blood-pressure, and syphilis may be merely coincident. The Wassermann reaction was performed in doubtful cases of our series, proving negative in twenty and positive in three. The first was a male of 67 with high blood-pressure, cardiac enlargement, and slight dilatation of aorta; there was also a branch bundle lesion. Digitalis changed flutter to fibrillation, and clinical improvement followed, but he died suddenly six months later. The second was a male of 55 with arteriosclerosis and cardiac enlargement, in whom the only evidence of syphilis was a positive Wassermann reaction. In the third patient flutter was a terminal complication of coronary occlusion of syphilitic origin, necropsy showing myocardial infarction and syphilitic aortitis and myocarditis.

Flutter in chronic rheumatic heart disease. Chronic rheumatic heart disease was present in 14 of our 52 cases (i. e. 27 per cent.). Seven had mitral stenosis alone, four mitral stenosis with aortic incompetence, two mitral disease without clinical signs of stenosis, and one aortic incompetence alone. In only half these rheumatic cases was a history of rheumatic fever or chorea obtained. Six patients (i. e. 43 per cent.) were females; indeed, rheumatism, acute or chronic, accounted for seven of the eight females in our series. Details of these cases are given in Table I. The onset of flutter usually proved of serious import, especially when it rapidly induced gross congestive failure. The following case may be cited to illustrate the disability due to flutter, and the benefit of restoring normal rhythm:

Ed Pearson

Case XI. Carpenter, aged 43. Rheumatic fever, aged 12. Well until 1923, when he had a sudden attack of palpitation, and had to cease work. No improvement followed two months' rest at home and hospital treatment. Seen six months after the onset of symptoms there was dyspnoea but no oedema. Heart enlarged, but no murmurs, though later signs of mitral stenosis and aortic incompetence became obvious. EC. showed flutter, with sometimes 1 : 1 and sometimes 2 : 1 rhythm (Fig. 5). Prolonged treatment with quinidine and digitalis restored normal rhythm; he improved and returned to work. Normal rhythm persisted for $2\frac{1}{2}$ years, during which he remained at work. Then he had a recurrence of flutter and was again entirely incapacitated. Normal rhythm was restored by further treatment and he has now been at work for six months.

Flutter in hyperthyroidism. Flutter is not uncommon in exophthalmic and toxic adenomatous goitre. Kerr and Hensel (23) found it ten times in 181 cases, compared with 29 instances of fibrillation; in 8 of these 10 it alternated with fibrillation. Krumbhaar (25), in 51 cases of goitre seeking surgical relief, observed 1 with flutter and 3 with fibrillation. In 377 consecutive cases of hyperthyroidism studied by Willius, Boothby, and Wilson (56) at the Mayo Clinic, there were 2 with flutter and 84 with fibrillation. Bickell and Frommel (3) observed 2 examples of flutter and 18 of fibrillation among 80 cases of goitre admitted to their clinic. Dameshek (10) reports 20 instances of fibrillation and 2 of flutter in 141 cases of goitre. Adding these results together we find that in

830 cases of hyperthyroidism, flutter occurred in 17, and fibrillation in 154; which is to say that fibrillation was only 9 times more frequent than flutter. Both disorders were often paroxysmal and then sometimes alternated in the same patient. We have observed the two following examples:

Case XLVII. Male, 25. First seen in April, 1922, with exophthalmic goitre. Heart not enlarged; no signs of failure. Pulse 136, irregular. Polygrams, flutter, A. 307, V. 122 (confirmed later by EC.). Digitalis induced fibrillation which persisted. In a year he returned with a recurrence of flutter and again digitalis induced fibrillation. In February, 1925, he was in fair health and doing light work.

Case XLVI. Male, 48. Seen in October, 1923, with exophthalmic goitre. Basal metabolic rate 140 per cent. EC. sinus tachycardia. A paroxysm of fibrillation occurred in hospital. In September, 1924, he returned to hospital with a rapid irregular pulse; EC. showed flutter, A. 324, V. 180. Normal rhythm was restored by treatment, and then the superior thyroid arteries were ligatured. Shortly afterwards partial thyroidectomy was performed, the pulse remaining regular. When last seen in March, 1926, he was greatly improved and at work, pulse regular, 90.

As long as thyrotoxaemia is active, normal rhythm is unlikely to be permanently restored. Before surgical treatment is undertaken an attempt should be made to abolish flutter, by quinidine if of recent origin, otherwise, or if quinidine fails, by digitalis. If fibrillation results it is preferable to flutter, and normal rhythm may yet return after operation (6). Even if flutter persists the patient will better bear operation after digitalization.

Flutter in high blood-pressure and chronic nephritis. Six cases are detailed in Table II. In none was there seen extreme cardiac enlargement on radioscopy. Five had some degree of heart failure when first seen in flutter. In hyperpiesis with failure the systolic pressure may fall to normal limits, and the pathological basis of the cardiac condition may then be obscure, as exemplified below.

Flowerday.

Case XV. Male, 51. No rheumatism or syphilis; W.R. negative. Congestive heart failure. Orthodiagram showed moderate cardiac enlargement (transverse diameter 16·2 cm., R. 6·7 cm., L. 9·5 cm.). EC., flutter, A. 250, V. 90, and left ventricular predominance. During flutter B.P. was constantly 140–120 systolic, 110–70 diastolic; on return of normal rhythm, B.P. 135/85. The cause of the cardiac enlargement was puzzling, but with normal rhythm a progressive rise of blood-pressure was observed, so that a year later it was 200/110, when the patient was greatly improved and at work.

Flutter in cardiac enlargement other than syphilitic, rheumatic, or hypertensive. Thirteen cases are detailed in Table III. The majority were elderly males in whom cardiac enlargement was probably due to arteriosclerosis and especially to coronary atheroma; several had bronchitis and emphysema. In none was there evidence of syphilis; in seven the Wassermann reaction was negative.

Case XXXI.[3] Male, 61. First seen in June, 1914. Dyspnoea and palpitation for a year, and unable to work for three months. No rheumatic history.

[3] It was on this patient that the circus rhythm was first demonstrated in clinical flutter by Sir Thomas Lewis (*Heart*, 1921, viii. 342).

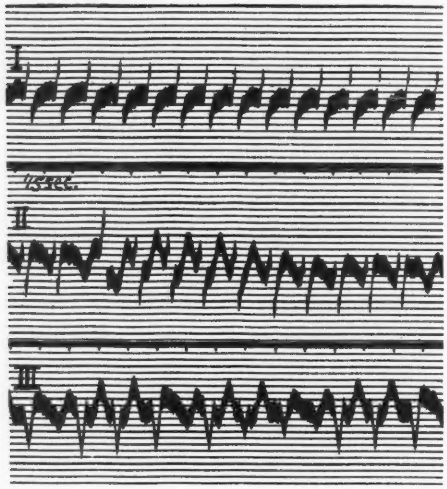

FIG. 3. EC. of first paroxysm of 1 : 1 flutter (Case XLV); lead I shows regular 1 : 1 rhythm, rate 285; leads II and III, slight irregularity of the ventricles and some aberrant ventricular complexes.

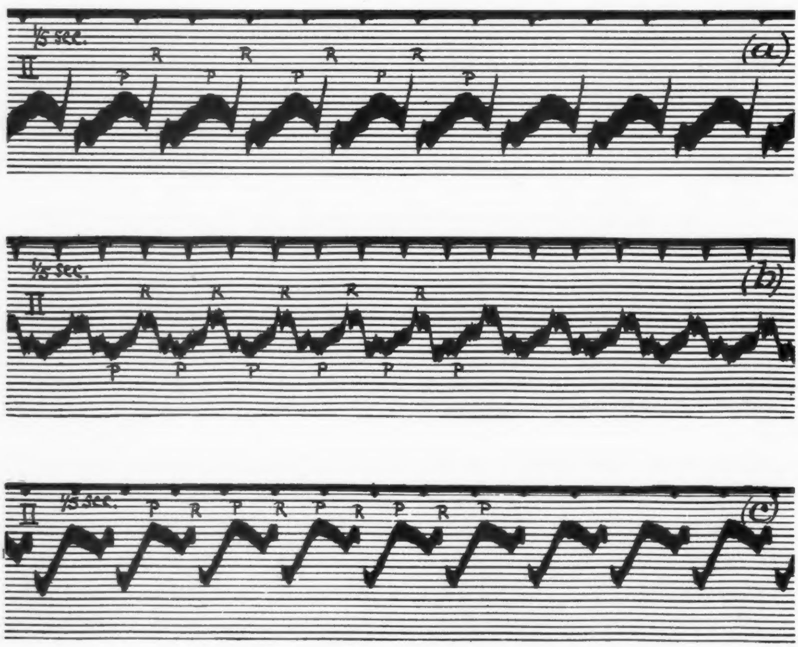

FIG. 4. EC.s showing slow flutter, with 1 : 1 rhythm, during quinidine. (*a*) Rate 198 (Case VII). (*b*) Rate 188 (Case XV). (*c*) Rate 181 (Case XLV).

W.R. negative. *Examination.* Cheyne-Stokes respiration, and signs of severe congestive failure. Radioscopy, moderate general cardiac enlargement. Duplicated first sound and a systolic murmur at apex. Arteries slightly thickened. B.P. 130, systolic. Pulse regular, 135, with alternation. EC., flutter, A. 270, V. 135. Digitalis produced a high degree of block, and failed to abolish flutter. He improved, and from 1914 to 1917 was able to do light work. He was again under regular observation from 1920, and all records have shown 2 : 1 flutter. When last seen in September, 1925, there was oedema, but he could walk about quietly. He died in July, 1926. It is remarkable that there was no recurrence of gross congestive failure during the twelve succeeding years of untreated flutter with a high pulse-rate, for he persistently refused drug treatment from 1914 till his death.

Flutter after acute coronary thrombosis. Three of our patients had paroxysms of flutter after typical attacks of coronary occlusion; in one this was verified by necropsy.

Case XLIX. Male, 44. Venereal disease aged 26; W.R. positive. Anginal attacks for two years, recently of daily occurrence. Aortic incompetence and slight dilatation of aorta. After several severe anginal seizures in bed, a paroxysm of fibrillation was recorded; at other times EC. showed flutter, A. 310, V. 155, and later a right branch bundle lesion. Normal rhythm returned next day. He had no further angina, but progressive heart failure led to death in a week. Necropsy, coronary occlusion from syphilitic changes, and recent and old myocardial infarction.

Case XLVIII. Male, 65. No previous angina. In August, 1924, he had a severe anginal seizure lasting two days; pericardial friction was heard, and the pulse became irregular. Polygrams showed flutter, and shortly after normal rhythm with prolonged *a-c* interval. He recovered, and two months later EC. showed normal rhythm and right branch bundle lesion. He died in January, 1926.

Case L. Male, 65. Had been treated for hypertension. Slight enlargement of heart and aorta (X-ray). Arteries thickened. B.P. 200–150 systolic. In November, 1925, while at stool, he had a sudden attack of severe sternal pain with sweating and collapse. Shortly after the onset polygrams showed flutter, but normal rhythm returned the same day. He recovered gradually and proceeded on holiday, but died suddenly a few months later. No necropsy.

Flutter is by no means a common event after coronary thrombosis; it has previously been reported by Willius and Barnes (55), Longcope (29), Drury (12), and Billings (5).

Flutter with 1 : 1 rhythm. During established flutter paroxysms occasionally occur in which the ventricles beat at the full auricular rate of 250–300 a minute. These paroxysms of 1 : 1 rhythm occurred spontaneously in two of our patients, and in two others they were recorded during quinidine treatment, though at lower rates. In Case XI four attacks were observed, the shortest lasting twenty minutes, the longest two hours. He never lost consciousness, but was compelled to sit down, complaining of pain about the left nipple shooting down the left arm. Fig. 5 shows a record of a paroxysm, rate 254 a minute. Case XLV had had two syncopal attacks, once injuring his head. He visited hospital during 1 : 1 flutter, rate 275 (Fig. 3), and four similar attacks were subsequently recorded during

quinidine treatment, at rates of 247, 181, 171, and 188 respectively. In the initial electrocardiogram aberrant ventricular complexes were seen in two of three leads, indicating exhaustion of conduction by the excessive speed. Case VII had two paroxysms of 1:1 rhythm during quinidine treatment (Fig. 4, *a*), and Case XV a single paroxysm, rate 188, with ventricular aberration (Fig. 4, *b*).

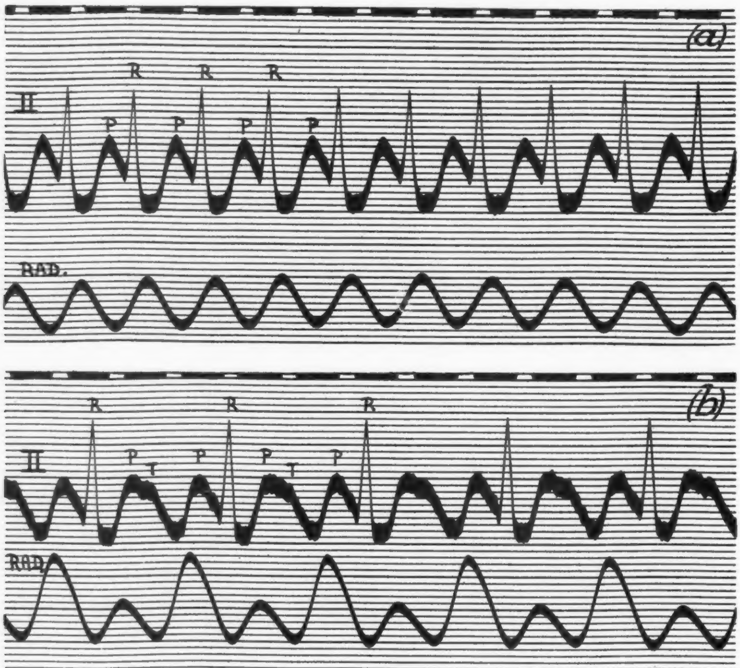

FIG. 5. EC. and radial pulse from Case XI: (*a*) during attack of palpitation, showing flutter with 1:1 rhythm, rate 254; (*b*) after cessation of palpitation, showing flutter with 2:1 block, A. 254, V. 127.

The symptoms which accompany these attacks vary greatly in severity, depending on the cardiac lesion even more than on the rate. When the auricles are slowed by quinidine to below 200 a minute, 1:1 rhythm need not produce severe symptoms. Exertion is often the exciting cause of these paroxysms (2, 33, 46, 59).

With regard to treatment, pressure on the vagus in the neck should be performed if symptoms are urgent. This had no effect in one of our patients, though it may give dramatic relief (6). In view of the relation of the paroxysms to exertion, the subject of them should be confined to bed until fully under the influence of digitalis. In both our cases quinidine was ultimately given without mishap, so it is not necessarily contra-indicated.

We know of only 18 reported instances of 1:1 flutter, namely by McMillan and Sweeney (33), Blackford and Willius (6), Lewis (27), Wedd (53), White and

Stevens (54), Gallavardin and others (15), Hart (18), Koplik (24), Mackenzie (30), Smith (46), Hewlett (20), Sachs (42), Poynton and Wyllie (40), Winterberg (59), and Bérard (2).

Flutter with complete heart-block. Case XVII. Male, 74. For two years slow pulse of 40–50 noted. Seen in September, 1924, with heart failure. Heart enlarged; systolic murmur at apex. Arteries normal. Pulse regular, rate 35. Polygrams showed flutter, rate 270, with a slow and regular ventricle, rate 35.

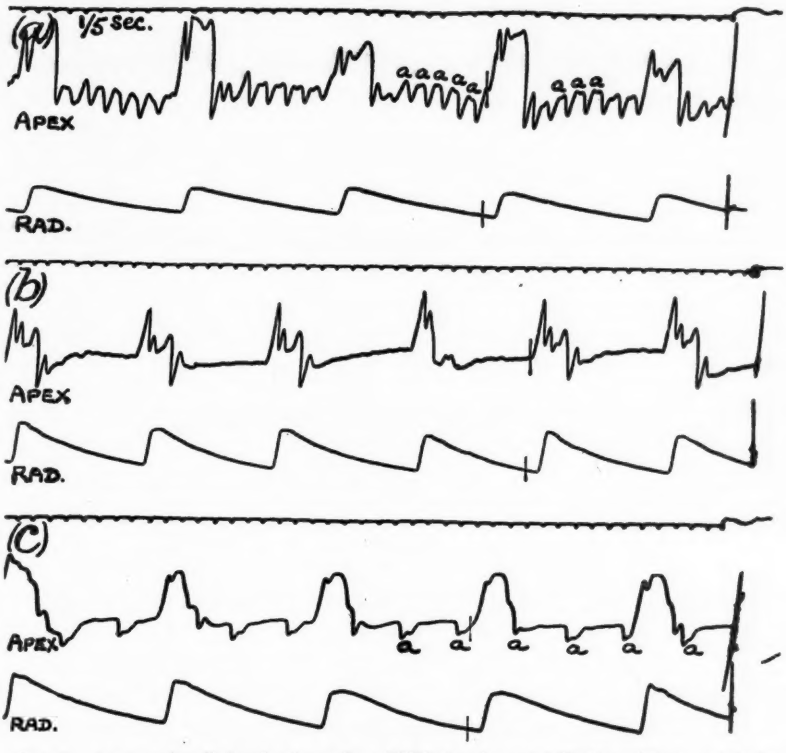

FIG. 6. Apex and radial pulse from Case XVII showing: (*a*) Flutter with complete heart-block, A. 270, V. 30. Before digitalis. (*b*) Fibrillation with complete heart-block, V. 30 a minute. After digitalis. (*c*) Sinus auricular rhythm, restored by digitalis, with complete heart-block, A. 82, V. 31.

The auricular sounds were clearly audible at the apex, and apex tracings showed auricular waves (Fig. 6). An EC. confirmed flutter. After digitalis treatment, records showed fibrillation with complete block (Fig. 6), and the auricles were no longer audible. Two days later polygrams proved the return of sinus auricular rhythm, still with complete block (Fig. 6). Auricular sounds were again heard, though not so loud as during flutter. Rapid improvement followed. When seen in February, 1925, and also in June, 1925, EC. showed an ectopic auricular tachycardia, rate 150, with inverted *P* waves; the ventricles slow as before (Fig. 7). He remained well until December, 1925, and died in January, 1926.

Eight other cases of flutter with coexisting complete heart-block have been recorded; namely by Ritchie (41), Blackford and Willius (6), Donzelot and Pezzi (11), Keating and Hajek (22), Vinnis (50), Wiltshire (58), Hall (17), and Schott

(43). Wiltshire's patient was subject to severe Adams-Stokes attacks, in some of which flutter occurred, in others sinus auricular rhythm. In none of the reported cases were symptoms attributed to the presence of flutter, though in our patient its abolition was attended with great improvement. Quinidine is scarcely indicated in complete block, and toxic effects have been reported after its use in cases of fibrillation with complete block.

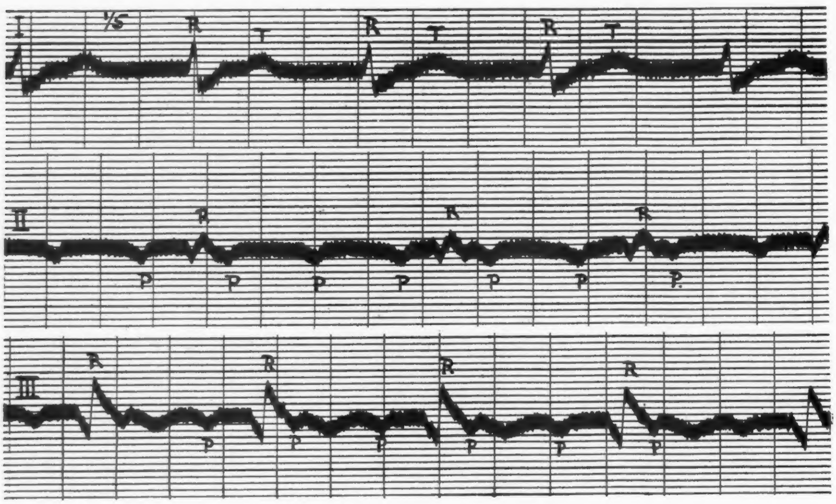

FIG. 8. EC. showing naturally slow flutter, A. 185, V. 92. The ventricular complexes are abnormal in all leads. (Case LI, before treatment.)

Lesser grades of defective conductivity are more commonly associated with flutter, for in four of our patients the ventricular rates were below 70 apart from digitalis. A persistent 4 : 1 degree of block may prove functional, as in Case XXIV, in which conduction was normal when sinus rhythm returned. Whereas 2 : 1 and 4 : 1 degrees of block are often stabilized in flutter, persistent 3 : 1 block is exceptional, though we have observed it occasionally.

The auricles in flutter and their reaction to drugs. Though the natural rate of the auricles in flutter almost always exceeds 200 a minute, it may fall far below this level as the result of quinidine. This raises the possibility of naturally slow flutter. In Case LI the auricular rate was constantly about 185 before any drug treatment. This man, aged 50, had signs of heart failure when first seen in flutter. There was cardiac enlargement without valvular disease ; W.R. negative. The history suggested a previous acute coronary thrombosis. The EC., seen in Fig. 8, shows slow flutter and abnormal ventricular complexes. Digitalis restored normal rhythm, which has now persisted for over eight months.

We have found spontaneous variations in auricular rate up to 30 a minute in records of the same case at different times. The rate may remain remarkably constant over long periods, and we can quote the recorded rates of the auricles in

Case XXXI over a period of ten years: June, 1914, 275; November, 1914, 245; March, 1922, 250; March, 1923, 257; December, 1923, 252; October, 1924, 254. The initial slowing may have been due to digitalis, but after 1914 no drugs were given. In Wiltshire's case, during Adams-Stokes attacks the auricles were observed to slow progressively from 240 to 165 a minute, accelerating again after a single vertricular systole. A gradual auricular acceleration from 150 to 240 a minute has also been described (38). Vagal pressure may slightly increase the auricular rate (7, 57), though we have not observed this. We have seen a slight fall in auricular rate after amyl nitrite in a patient who took this for angina.

Digitalis has a dual action on the auricle—a vagal effect, which increases the rate, and a direct effect on the muscle, which decreases the rate. In clinical flutter digitalis may fail to affect the auricular rate, or may cause slight acceleration or slight slowing. In 16 cases, where sufficient records before and during digitalis were available, we found increase in rate in two cases, slight decrease in rate in 5, and no change in 9.

Quinidine always slows the auricles in flutter. In 5 cases we recorded auricular rates below 200 a minute, the lowest being 142. This slowing passes off completely within 24 hours of the drug being stopped. Fig. 9 shows an example of slow flutter under quinidine, and also aberrant ventricular complexes. In Fig. 10 the effect of digitalis and quinidine on auricular rate in Case XI is charted.

The shape of the *P* waves varies in different cases, but it remains constant in each individual case. They may be undulating with both up-strokes and down-strokes blunted, or sharply pointed upwards, downwards, or in both directions, giving a 'zigzag' appearance. Bifid *P* waves occurred in Case III, and slight notching of the down-strokes was not uncommon.

Auricular waves may also appear in apex tracings (Fig. 6). In Fig. 11 the jugular waves suggest auricular alternation.

The ventricles in flutter. The ventricular complexes in electrocardiograms are usually of the normal supra-ventricular type. Aberrant ventricular complexes are not uncommon, especially after quinidine (Fig. 9), or during periods of 1 : 1 rhythm (Fig. 3). Ectopic ventricular beats can occur during flutter (see Gallavardin (13)). Digitalis bigeminy from extra-systoles also occurs (Fig. 12), though less commonly than during fibrillation, and we have seen a similar coupling from quinidine. Usually, however, bigeminy in flutter is due to alternate 2 : 1 and 4 : 1 block, or occasionally 2 : 1 and 3 : 1 block, when the radial may be evenly spaced (Fig. 1).

Diagnosis.

In 2 : 1 flutter the pulse-rate is almost always between 120 and 160 a minute, whereas in paroxysmal tachycardia rates above 160 are common. A duration of more than a fortnight is strongly in favour of flutter. It must be emphasized, however, that a regular pulse is naturally present in only about half the cases of

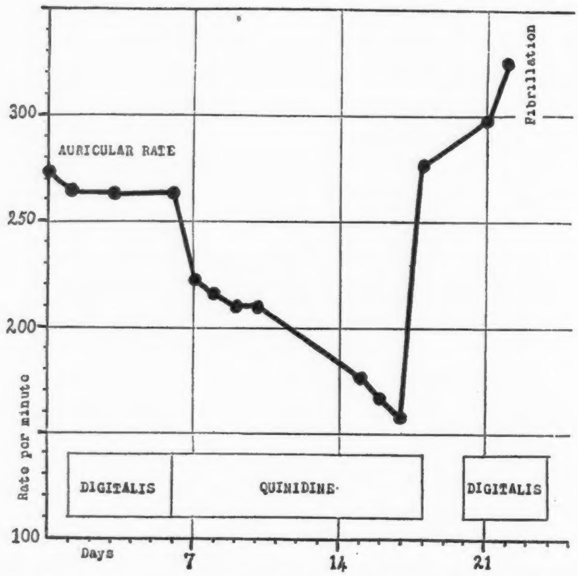

FIG. 10. Curve showing the auricular rate in a case of flutter under treatment by digitalis (tincture, one drachm daily) and by quinidine (total 305 grains). (Case XI.)

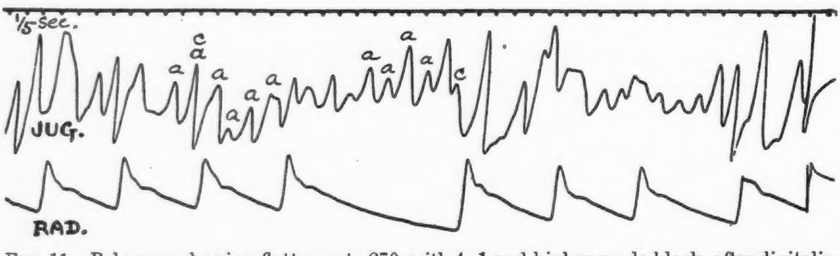

FIG. 11. Polygram showing flutter, rate 270, with 4 : 1 and higher grade block, after digitalis. Alternation of the auricular waves is seen during the long ventricular pause.

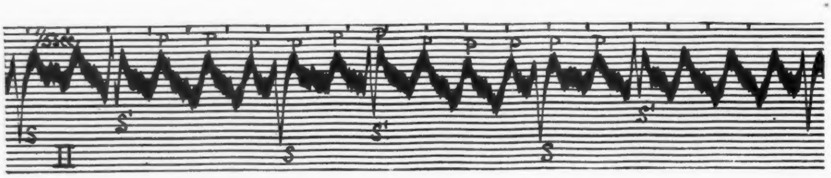

FIG. 12. EC. showing flutter with digitalis coupling. (Case XLV.)

flutter. Where the pulse is irregular the distinction from fibrillation may be impossible clinically, but often periods of regularity can be detected in flutter. A test exercise will often cause an irregular pulse to become rapid and regular at a rate of 120–160. Vagal pressure during digitalis administration will usually induce long pauses of the pulse. Inspection of the jugular pulse in the neck is seldom a help in distinguishing flutter from paroxysmal tachycardia. Flutter may be recognized during radioscopic examination, when the ventricles are slow, as in our Case III.

We have taken polygraphic records in nearly every case, checking their interpretation by electrocardiograms. Diagnostic polygrams of flutter are perhaps more difficult to obtain than electrocardiograms, but the polygraphic method has great importance if only by virtue of its wider applicability. Contrary to the assumption of some writers, we assert that flutter can often be diagnosed with certainty by the polygraph alone. Diagnostic polygrams were obtained in the large majority of our cases, if not initially, then after digitalis. Polygrams of 2 : 1 flutter are not diagnostic except in conjunction with other records showing higher grades of block, as identical curves may often be obtained in paroxysmal tachycardia and rapid normal rhythm. Lewis has stressed the value of 'spacing' in radial tracings from flutter, and this is often conclusive. We have, however, pulse tracings from flutter where a distinction from auricular fibrillation seemed impossible, and even in electrocardiograms the degree of block may be completely irregular. Occasionally curves of 2 : 1 flutter, in which alternate *P* waves are buried in the ventricular complexes, may be difficult to distinguish from simple tachycardia, but subsequent records will often show a variation in block which is diagnostic.

After-history and Prognosis.

We have succeeded in following up all our cases after the completion of treatment, either until death or until 1926. After doing this we have come to the conclusion that too rosy a view of the prognosis in flutter is suggested by some writers. We have attempted to assess the disability due directly to flutter in the various types of case, and especially the relative disadvantage to the patient of flutter and fibrillation respectively. Flutter often precipitated heart failure in patients with heart disease who previously had been in fair health; in some patients cessation of work was directly attributable to the onset of flutter. We have seen flutter produce a severe degree of disability and total incapacity for work in patients with a heart little diseased, and where the return of sinus rhythm has almost or completely restored the normal capacity for effort (*vide* Cases XI, XV, XXXIII, XXXV, XXXVIII). The onset of continuous flutter appears to us a more serious event than the onset of fibrillation, at least in the majority of cases. We are satisfied that a change from flutter to fibrillation is almost always beneficial to the patient; ambulant cases of fibrillation are more easily controlled by digitalis, and are not liable to the abrupt doubling of ventricular rate which often follows exertion in flutter.

Of the 52 cases 29 have died, comprising 20 of the 40 cases with established flutter, and 9 of the 12 with paroxysmal flutter.

Established flutter. Of 40 cases, normal rhythm returned under treatment and was maintained in 20. Twelve of these are still alive and 8 have died. Of those alive 4 have so far survived 4 years or longer and 5 from 1 to 4 years. Normal rhythm is still present in all except Case XXXII, where it was recorded for six months, but three months later there was fibrillation. Case XI, after being at work for over two years with normal rhythm, recently had a recurrence, but normal rhythm has again been restored. Seven patients are able to work, 3 others are well and able to get about, and 2 are incapacitated by hemiplegia. Of the dead, 4 died within six months, and all but 1 within two years of the first recognition of flutter. The cause of death in 3 was entirely unconnected with the heart: Case XXVIII succumbed to influenza, after being at work for two years with normal rhythm; Case XXXVIII remained well for five years except for one relapse, and died of malignant disease; Case XLIII died of pulmonary tuberculosis. Three died from uncomplicated failure, 1 after pulmonary infarction, and one suddenly.

Of 11 cases in which fibrillation was finally established, 6 are still alive and 5 have died. Of those alive, 1 has so far survived seven years, 4 for two to five years, and 1 nine months, reckoning from the first recognition of flutter. Only 1 is at work, though the rest are free from gross failure and able to get about. Of those dead, 3 died within six months, and all within eighteen months.

Of 9 cases in which flutter persisted in spite of treatment, 7 have died and 2 are still alive. Four died within six months, 2 after one to two years, and 1 after twelve years. Uncomplicated failure was the cause of death in 5; 1 died from septicaemia, and 1 suddenly from a cause unknown. Of those alive, 1 has so far survived two years, and 1 eighteen months; the latter is free from serious symptoms and does some clerical work.

Paroxysmal flutter. Of 12 cases, 9 have died and 3 are still alive: Case XXXVI after six years, Case VIII after four years, and Case LII after one year from the first recognition of flutter. In several cases prolonged paroxysms were ended by digitalis or quinidine, and it is probable that in these flutter would have become established but for treatment. In Case V fibrillation was observed before death, but others died with normal rhythm. The high mortality was due entirely to the serious underlying heart lesions with which the paroxysms happened to be associated, e. g. infective endocarditis, coronary thrombosis.

Prognosis. Prognosis depends upon the underlying cardiovascular lesion, the tolerance shown to the abnormal rhythm, and the response to treatment. Where the expectation of life is in any case short, as in infective endocarditis, flutter may be no more than a terminal complication, and treatment will scarcely affect the outlook. Where the heart seems otherwise healthy, the prognosis is not in terms of life and death, but of the relief of symptoms and restoration of capacity for work. With moderate degrees of heart impairment flutter is an embarrassment likely to induce failure and thus to shorten life; it is here that

the response to treatment of the flutter itself so greatly influences prognosis. The type and severity of heart lesion is no guide to the reaction of fluttering auricles to digitalis or quinidine, for digitalis may restore normal rhythm in a moribund patient (Case XLII) and yet may fail in a comparatively healthy one (Case XXXI). We know that taking all cases the chances are about three to one in favour of flutter being displaced. If the rhythm has been changed one must still estimate the clinical effects of such a change before giving a final prognosis. Paroxysms of flutter rarely prove directly fatal; they are, however, occasionally followed by embolism. Nothing can entirely prevent their recurrence, but prolonged attacks can usually be ended by digitalis or quinidine.

Speaking generally, the most important guide to prognosis before treatment is the degree of tolerance shown to flutter, i. e. whether or not it rapidly induces congestive heart failure. Thus of 22 patients with established flutter who had signs of failure when first seen, 17 have died and 5 are still alive, 10 dying within six months; whereas of 18 patients free from signs of failure when first seen, only 3 have died and 15 are still alive.

From a consideration of the after-histories of the whole series we conclude that a useful existence is seldom possible unless normal rhythm is restored and maintained. Where treatment results in established fibrillation capacity for work is unlikely to be attained, though these patients may remain free from failure and relatively comfortable for long periods, having an expectation of life which is better than when flutter continues.

Treatment.

Details of treatment are tabulated. Table A includes those cases which received digitalis only; Table B, those who had quinidine, with or without digitalis at other times. Both paroxysmal and established cases are included. The results given represent the final rhythm after the completion of all treatment, the rhythm still persisting in surviving cases unless otherwise stated. Digitalis and quinidine were never given simultaneously, though they were often given consecutively to the same case; their effects are therefore considered separately.

Digitalis. It is well known that digitalis can convert flutter into fibrillation and that, if the drug is then withheld, normal rhythm returns in a proportion of cases. In flutter more than in any other condition full doses of digitalis are essential; it may be necessary to press the drug repeatedly until toxic effects appear, before success is obtained. Our routine was to give tincture of digitalis, B.P., by mouth in doses amounting to one drachm (3·5 c.c.) daily. Occasionally two drachms daily were given for short periods, but we did not find this an advantage over the more prolonged administration of a drachm daily, continued if necessary for two to four weeks, and to a total consecutive dosage of 30 drachms (107 c.c.). Where Nativelle's digitalin was used we have assumed that three white granules (each of 1/240 grain) are the equivalent of one drachm of the tincture, though sometimes both toxic and therapeutic effects were more readily

obtained by the granules. Digitalis was continued for 12–24 hours after the appearance of fibrillation and then stopped. Normal rhythm may, however, return while digitalis is still being taken, with or without a recognized period of fibrillation (Cases XLII, VII, XV, XXXVIII, XX). Where digitalis had to be withdrawn while flutter was still present, we have seen the change to fibrillation after an interval of a few days. When full doses of digitalis in hospital failed to remove flutter, prolonged administration of moderate doses was occasionally effective. For example, Case XV received 31 drachms of digitalis in twenty-three days, followed by Nativelle's digitalin for four days, without effect, and left hospital in flutter, but after taking a drachm daily for a month normal rhythm was found and has persisted. In Case XLV both quinidine and digitalis failed in hospital, but half a drachm of digitalis daily for ten weeks induced fibrillation.

The *final* results obtained in 20 cases treated by digitalis alone were as follows:

Normal rhythm	9 cases
Nodal rhythm	1 case
Fibrillation	4 cases
Flutter persisted	6 cases

Adding 16 cases from Table B in which quinidine was ineffective or was only used after digitalis had established fibrillation, we obtained the following results from digitalis in 36 cases:

Normal rhythm	13 cases.
Nodal rhythm	1 case.
Fibrillation	13 cases (3 later converted later to normal rhythm by quinidine).
Flutter persisted	9 cases.

Thus in a quarter of the cases flutter was unaffected, and of the remainder half persisted in fibrillation, half reverted to normal rhythm. Recurrences, details of which are given in the tables, were fairly common: but fortunately where digitalis has once arrested flutter it will do so a second time, though the chances of restoring *normal* rhythm a second time are diminished. We did not find flutter more amenable to digitalis in one type of heart lesion than in another, and the results in the rheumatic and senile groups were much the same.

Strophanthin. Where symptoms of heart failure are urgent intravenous strophanthin is a rapid means of obtaining a digitalis effect. In Case XLVIII with myocardial infarction the injection of 1/200 grain (0·3 mg.) strophanthin was followed the next day by return of normal rhythm. In Case VI two injections (1/200 and 1/100 grain) terminated flutter which had lasted two days, though they did not affect the pulse-rate during flutter. In Case XVIII two intravenous injections of 1/100 grain of strophanthin caused fibrillation, and in six days normal rhythm returned without any other drug treatment. A single intravenous injection of gr. 1/100 in Case XXXI halved the pulse-rate, increased the secretion of urine, and alleviated the symptoms considerably, without affecting the flutter.

Quinidine. Much has been written of quinidine sulphate in the treatment

of fibrillation, but little of its use in flutter, where its value in comparison with digitalis has to be decided. We have tested its possibilities in twenty-one patients, at one stage or another. After a tentative dose of 5 grains (0·3 grm.) on the first day, the dose was increased daily by 5 grains until 30 or even 40 grains daily were reached, a dose which was maintained if necessary for several days. Of fifteen cases where quinidine was given during established flutter, it induced normal rhythm in three and failed to change the rhythm in twelve. One of the successful cases had paroxysms subsequently, but quinidine always ended them, and for three years has prevented the return of continuous flutter. Of three cases of paroxysmal flutter, quinidine diminished and shortened the attacks in two and merely shortened them in one. In six cases, after digitalis had produced fibrillation which persisted, quinidine restored and maintained normal rhythm in three and caused a return to flutter in three. In these last digitalis again abolished flutter, though this cannot always be expected, for Wolferth (60) and Viko and others (49) have recorded instances of fibrillation where quinidine produced 'fixed flutter' which resisted all further treatment.

To sum up, in twenty-one cases where quinidine was employed, it was useful in nine, but in only six of these actually during flutter, and in only three in non-paroxysmal flutter. Hence we cannot subscribe to Wolferth's opinion that quinidine is about as successful in flutter as in fibrillation. Instances of flutter successfully treated by quinidine have been reported by Wedd (52), Volle (51), Gallavardin and Gravier (16), Lian (28), Wilson (57), and Arnell (1), but in numbers insufficient to decide the general proportion of successes to failures. No serious toxic symptoms resulted from quinidine in the doses mentioned, nothing beyond headache, nausea, and occasional vomiting. Frequent aberrant ventricular complexes were sometimes recorded.

What are the relative advantages of *quinidine* and *digitalis* in the treatment of flutter? Quinidine will restore normal rhythm in a proportion, in our series 1 in 5, and the intermediate stage of fibrillation is avoided. If successful quinidine may be continued indefinitely in small doses as a prophylactic against recurrence. Where digitalis has changed flutter to fibrillation only, quinidine may then carry the change farther to normal rhythm. An unsuccessful course of quinidine is no bar to a subsequent and successful course of digitalis. In paroxysmal flutter it will often diminish the frequency of attacks and bring an individual attack to an end.

Digitalis will restore normal rhythm, with or without an observed stage of fibrillation, in a higher proportion, in our series 1 in 3, without the use of quinidine at all. Apart from restoration of normal rhythm digitalis will change flutter to permanent fibrillation in another third, a change almost always beneficial to the patient. Digitalis has an enormous advantage over quinidine in virtue of its beneficial effect on cardiac efficiency from the first, irrespective of change in rhythm.

The restoration of normal rhythm, whether effected by digitalis or quinidine, is attended with a slight risk of precipitating embolism in patients who are

liable to it by reason of intra-cardiac thrombosis. Such a possibility cannot deter us from treating a patient with flutter. If normal rhythm is restored this risk will be the same whether digitalis or quinidine is used, but it is absent where digitalis does no more than induce fibrillation. There remains the question of the relative toxicity of digitalis and quinidine; there is no doubt that quinidine is more easily toxic than digitalis, and a few deaths have been ascribed to it apart from embolism. Unlike digitalis, quinidine can only benefit the heart by restoring its rhythm, and it may even aggravate failure by its action on the myocardium.

We venture to think that in a young subject with a heart relatively healthy and with flutter or recent origin, the return of normal rhythm is so important that quinidine should be given a trial before digitalis. In such a case the risks from quinidine in proper doses are negligible. Apart from this type of patient, we think that digitalis should be the first choice. If normal rhythm is not restored but fibrillation is induced, quinidine may then be used in the hope of restoring normal rhythm in suitable cases. Thus it may be considered where the heart is not greatly enlarged, failure is absent, and there is no history of embolism. Though there are contra-indications to quinidine in flutter, digitalis is never contra-indicated.

After-treatment. In the treatment of patients after the abolition of flutter, rest is of the utmost importance, for exertion can precipitate flutter in predisposed individuals. After the restoration of normal rhythm at least a week should be spent strictly in bed and a month should elapse before ordinary physical exertion is allowed. The return to normal activity should even then be gradual. Where quinidine has restored normal rhythm the dose should be gradually reduced; five grains thrice daily should be taken for a week, followed by five grains twice daily for six months or more. No ill effects seem to result from its prolonged administration even for years.

Summary and Conclusions.

Fifty-two hitherto unpublished cases of auricular flutter are recorded and their clinical features, treatment, and after-histories are described or tabulated. Flutter is usually an established rhythm when first diagnosed, and is unlikely to cease or to change to fibrillation spontaneously. In about 25 per cent. of all cases it is paroxysmal and remains so, though it often alternates with paroxysms of fibrillation.

Flutter most commonly occurs in middle age or later; in our series the maximum incidence was between 40 and 50, though it was almost equally frequent in each decade between 40 and 70. Males are affected about ten times as frequently as females, though in rheumatic heart disease the sex incidence is more nearly equal. Flutter is most often associated with chronic rheumatic heart disease or with cardiac enlargement in elderly males; less often it complicates high blood-pressure, hyperthyroidism, acute febrile conditions, coronary thrombosis, or syphilis. Its clinical associations are thus similar to those of fibrillation,

though rheumatic infection is not nearly so predominant in its aetiology. Occasionally, like paroxysmal tachycardia and extra-systoles, flutter is the only evidence of cardiac abnormality—no more than a functional disturbance. Flutter is by no means limited to the final stages of heart disease: witness the moderate degree of heart enlargement usually found, and the duration of life possible after its onset in favourable cases, and those responding to treatment.

A regular pulse is naturally present in only about half. The systolic blood-pressure is not specially low during flutter, though a slight rise often occurs on the return of normal rhythm. Diastolic pressure may be relatively high during flutter, and will then fall with the onset of normal rhythm. A fall of blood-pressure in flutter with heart failure may mask an underlying hyperpiesis.

Extreme acceleration of the ventricles to 250–300 a minute, from the assumption of 1 : 1 *a.-v.* rhythm, may occur during established flutter, spontaneously, after exertion, or from quinidine; such attacks were recorded in four patients. Complete heart-block with auricular flutter is also described.

Diagnosis by polygraph is usually possible, especially if records at different stages are obtained, though the electrocardiograph is the instrument of choice. A regular tachycardia with a fixed rate between 120 and 160 a minute which persists for over a fortnight is almost certainly flutter.

The results of treatment by digitalis, strophanthin, and quinidine are detailed. Digitalis removes flutter far more often than does quinidine. Digitalis alone restores normal rhythm in over a third of cases, and in another third it induces fibrillation. Quinidine converts flutter directly to normal rhythm in about one case in five; it often cuts short paroxysms of flutter, though continued small doses do not entirely prevent their recurrence. Where digitalis has left fibrillation, quinidine may convert this to normal rhythm. The indications for digitalis and quinidine respectively are discussed.

The prognosis depends on the underlying heart lesion and on the reaction of the superimposed flutter to treatment. When the onset of flutter rapidly induces congestive heart failure the expectation of life is far less than in the absence of failure. Where the heart otherwise is relatively healthy flutter greatly diminishes physical capacity and may even induce failure, but striking improvement is to be expected from treatment.

All cases were followed up after the completion of treatment, many for considerable periods. The after-histories emphasize the advantage of the restoration and maintenance of normal rhythm, which alone is likely to permit a return to work. Lesser improvement may be expected after the change from flutter to fibrillation. Where flutter persists in spite of treatment, there is great incapacity and a higher mortality.

We are indebted to Dr. R. A. Young, Dr. A. J. Whiting, Dr. C. E. K. Herapath, and Dr. J. W. McNee for kindly allowing us to use Cases XLVI, II and XXXIX, XXXV, and XXIII respectively, as these patients were under their care. We wish to thank Dr. John Grimshaw for his valued help with the text.

Table I.

Chronic Rheumatic Heart Disease.

Case.	Age and Sex.	Valve Lesion.	Congestive Failure.	Probable Duration before Treatment.	Ultimate Rhythm.	After-history.
I	F. 41	M. S., A. I.	+	Unknown	Fib.	Died in 3 months, with failure
II	M. 49	M. S.	+	2 months	N. R.	Died in 10 months, pulmonary embolism
III	M. 42	M. S.	0	5 months	Fib.	Alive and well after 5 years. Unable to work
IV	M. 38	M. S., A. I.	0	Paroxysms, 1 month	N. R.	Resumed work. Died in 4 years
V	F. 44	M. S.	+	Paroxysms, 3 months	Fib.	Died in 6 months, cerebral embolism
VI	F. 29	M. S.	0	Paroxysmal	N. R.	Died in 2 months
?? Hooper — VII	M. 48	M. S.	0	Unknown	Fib.	Alive after 3 years. Unable to work
VIII	F. 49	M. S., A. I.	0	Paroxysmal	N. R.	Alive after 3 years. Cerebral embolism
IX	M. 60	A. I.	+	1 month	Flutter	Died in 3 months
X	F. 56	M. I.	+	10 months	Fib.	Died in 6 months, with failure
Pearson — XI	M. 43	M. S., A. I.	0	5 months	N. R.	Alive and at work after 3 years. One recurrence
XII	M. 49	M. I.	+	Unknown	Flutter	Died in 2 years, with failure
XIII	F. 30	M. S.	+	Unknown	Flutter	Died in 4 months, with failure
XIV	M. 32	M. S.	+	Unknown	Fib.	Died in 16 months, with failure

Table II.

High Blood-pressure or Chronic Nephritis.

Case.	Age and Sex.	Clinical Diagnosis.	Congestive Failure.	Probable Duration before Treatment.	Ultimate Rhythm.	After-history.
Flowerday — XV	M. 51	Hypertension	+	2 months	N. R.	Alive and well after 1½ years. At work
XVI	M. 49	Art.-scl.	0	10 months	Flutter	Alive and well after 2 years
XVII	M. 74	Hypertension, C. H-B.	+	Unknown	Sinus rhythm, C. H-B.	Improved. Died in 15 months
XVIII	M. 56	Chronic nephritis	+	6 months	N. R.	Died in 6 months, with failure
XIX	M. 49	Hypertension, art.-scl.	+	8 days	N. R. for 1 year, Fib.	Died in 17 months, with hemiplegia
XX	M. 68	Hypertension	+	3 weeks	N. R.	Improved. Alive and well after 1 year

Abbreviations employed in Tables:

M. S. = mitral stenosis.
A. I. = aortic incompetence.
N. R. = normal rhythm.
M. I. = mitral incompetence.
Fib. = fibrillation.
C. H-B. = complete heart-block.

TABLE III.

Cardiac Enlargement, without High Blood-pressure or Syphilis.

Case.	Age and Sex.	Associated Condition.	Congestive Failure.	Probable Duration before Treatment.	Ultimate Rhythm.	After-history.
? Carne XXI	M. 51	Chronic bronchitis	+	3 months	Fib.	Alive after 6 months. At light work. Spontaneous at first and Q → Flutter Dig → Fib.
XXII	M. 44	Chronic pericarditis	+	Paroxysmal, 5 years	N. R.	Died in 2 months, with failure
XXIII	M. 60	—	0	Unknown	N. R.	Improved. Under observation
XXIV	M. 76	Angina pect. Emphysema	0	Unknown	N. R.	Alive after 6 months, cerebral embolism
XXV	M. 56	Chronic bronchitis	+	1 year	Flutter	Alive after $1\frac{1}{2}$ years. Unable to work
XXVI	M. 66	—	+	Unknown	Flutter	Died suddenly in 1 week
XXVII	M. 62	Angina pect.	+	Unknown	N. R.	Died in 5 months
XXVIII	M. 27	—	0	7 months	N. R.	Resumed work. Died in 2 years from influenza
XXIX	F. 63	Intermittent claudication	0	6 months	N. R.	Died suddenly in 1 week
XXX	M. 62	Albuminuria	+	2 months	Flutter	Died in 14 months, with failure
XXXI	M. 61	Bronchitis	+	1 year	Flutter	Died in 12 years. Flutter persisted
XXXII	M. 53	Bronchitis	0	3 years	Fib.	Cerebral embolism after N. R. Alive after 4 years
XXXIII	M. 48	Obesity	0	8 months	N. R.	Alive after 15 months. Able to work

TABLE IV.

Remaining Cases.

Case.	Age and Sex.	Associated Condition.	Congestive Failure.	Probable Duration before Treatment.	Ultimate Rhythm.	After-history.
XXXIV	M. 52	? influenza	0	2 weeks	N. R.	Alive and well after 3 years. Recurrences
XXXV	M. 18	? influenza	0	6 months	N. R.	Alive after 4 years. Able to work. Plays football
XXXVI	M. 67	—	0	Paroxysms 2 years	N. R.	Alive and well after 6 years. Paroxysms occur
XXXVII	M. 33	—	0	Unknown	Fib.	Alive after 7 years. Able to work
XXXVIII	M. 65	Enlarged prostate	+	3 days	N. R.	Well for 5 years. Died of malignant disease
XXXIX	F. 19	Acute rheum. A. I., M.S.	0	Unknown	N. R.	Improved. Died in $3\frac{1}{2}$ years from acute carditis
XL	M. 15	Acute rheum. Pericarditis. A. I.	0	Unknown	N. R.	Alive after 4 years. Able to work
XLI	M. 32	Empyema. Septicaemia	+	Unknown	Flutter	Died in 4 months, with failure and septicaemia
XLII	M. 34	Infect. endoc. Pericarditis. Nephritis (P.M.)	+	Paroxysmal	N. R.	Died in 2 months, with failure
XLIII	M. 56	Art.-scl. Pulm. tuberc.	0	1 year	N. R.	Died in 2 months from pulmonary tuberculosis
XLIV	M. 67	Hypertension. W. R. +	0	3 days	Fib.	Improved. Died in 6 months
XLV	M. 55	Art.-scl. W. R. +	0	Unknown	Fib.	Alive and well after $2\frac{1}{2}$ years. Unable to work
XLVI	M. 48	Exophth. goitre	0	Unknown	N. R.	Alive after 2 years. Able to work
XLVII	M. 25	Exophth. goitre	0	Unknown	Fib.	Alive and well after 3 years
XLVIII	M. 65	Coronary thrombosis. Glycosuria	0	3 weeks	N. R.	Died in $1\frac{1}{2}$ years
XLIX	M. 44	Myocardial infarction. W. R. + (P.M.)	Angina	Paroxysmal	N. R.	Died in 1 week, with failure
L	M. 65	Hypertension. Coronary thrombosis	0	2 hours	N. R.	Died in 2 months
LI	M. 50	Old coronary thrombosis ?	+	Unknown	N. R.	Alive and well after 8 months
LII	M. 12	Congenital heart disease	0	Paroxysm	Ectopic tachyc.	Alive and well after $1\frac{1}{2}$ years

Selman —

TABLE A.

Treatment: Digitalis only.

Case.	Digitalis (Drachms of Tincture).	Result.
I	6	Fib.
	Recurrence	
	8	Fib.
	Recurrence	
	4	Fib.
IX	9, 9	Flutter
X	8	N. R.
	Recurrence	
	7	Fib.
XII	10	Flutter
	Further digitalis	Flutter
XIII	7	Flutter
	Strophanthin and further digitalis	Flutter
XIV	7	Fib.
XVII	16	Fib. (C. H-B.), N. R. (C. H-B.)
XX	5	N. R.
XXIII	8	Flutter
	Small doses	
	2 months	Nodal rhythm
XXIV	14, 2	Fib., N. R.
XXVI	7	Flutter
XXVIII	11, 11, 10	N. R.
XXX	10	Flutter
	Refused further treatment	
XXXI	23, 8	Flutter
	(toxic symptoms)	
XXXVIII	4, 3	N. R.
XXXIX	13	N. R.
XLII	4	Fib.
	5	N. R.
XLIII	32	Fib.
		N. R.
	Recurrence	
	7	N. R.
XLIV	10	Fib.
LI	14	N. R.

Table B.

Treatment: Quinidine, or alternate Quinidine and Digitalis.

	Case.	Treatment (Drachms of Tinct. Digitalis: Grains of Quinidine).	Result.
	II	Q. 36, Q. 144 (toxic) D. 15	Flutter N. R.
	III	D. 3, D. 9 Q. 1426 D. 6	Fib. Flutter Fib.
?? Harper –	VII	Q. 220 D. $\frac{1}{2}$ drachm daily for 8 months	Flutter Fib.
	VIII	Q. 20 daily in paroxysms	N. R.
Pearson –	XI	D. 5, Q. 305, D. 4 Q 105 Recurrence after $2\frac{1}{2}$ years, Q. 165, D. 12, Q. 15	Fib. N. R. N. R.
Flounday –	XV	Q. 140, D. 31, D. 4, D. 28	N. R.
	XVI	Q. 195, D 7, Q. 80	Flutter
	XIX	Q. 145, D. 3	N. R.
	XXII	Paroxysms of fib. and flutter, Q 132, D. 3	N. R.
	XXV	Q. 295, D. 23 Further digitalis	Flutter Flutter
	XXXII	D. 8 Q. 15 4 years later	Fib. N. R. Fib.
	XXXIII	Q. 95	N. R.
	XXXIV	Q. 30	N. R.
	XXXV	D. 7, Q. 75, D. 15	N. R.
	XXXVI	In paroxysms, Q. 10 daily	N. R.
	XXXVII	Frequent courses of digitalis Q. 230	Nodal rhythm, Fib. Flutter, Fib.
	XL	D. 4, 14, Q. 110 (toxic)	N. R.
	XLI	Q. 35 (toxic), D. 32	Flutter
Selman –	XLV	D. 13, Q. 135, Q. 290, D. 4, Q. 220, D. 4, Q. 155, D. 35 Q. 330 D. 7	Fib. Flutter Fib.
	XLVI	Q. 180, D. 5 Q. 80	Fib. N. R.
	XLVII	Q. 50, D. 12 Recurrence after one year. Digitalis	Fib. Fib.

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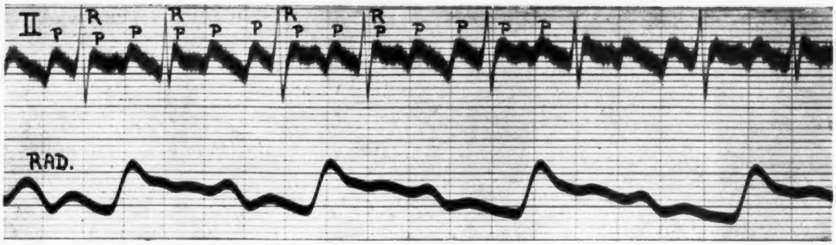

FIG. 1. Electrocardiogram and radial pulse showing flutter with alternate 2 : 1 and 3 : 1 block. The radial is regularly spaced and indistinguishable from pulsus alternans. A. 300 ; V. 120. (Case XX.)

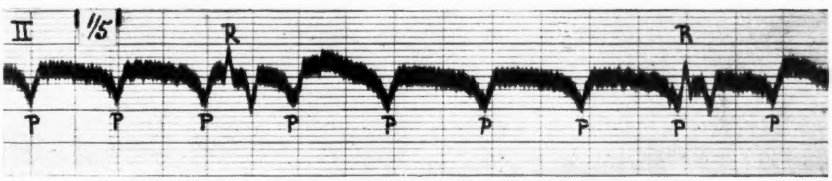

FIG. 7. EC. showing an ectopic auricular tachycardia, rate 150, and complete heart-block. (Case XVII.)

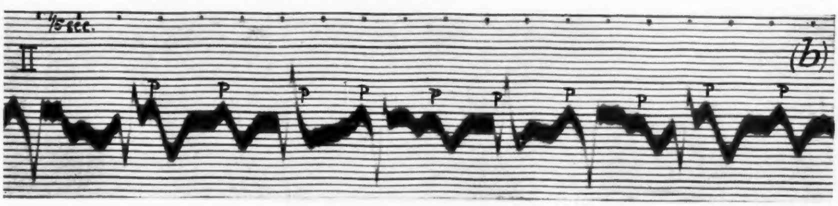

FIG. 9 Slow flutter from quinidine ; auricular rate 165, and aberrant ventricular complexes. (Case XLV.)

ON CERTAIN ABNORMALITIES, CONGENITAL AND ACQUIRED, OF THE PULMONARY ARTERY[1]

By R. C. CLARKE, C. F. COOMBS, G. HADFIELD, and A. T. TODD

With Plates 2–5

Introduction.

If the earlier morbid anatomists had anything to say of the acquired lesions of the pulmonary artery and its branches, it was only by way of comparing the extreme rarity of such lesions with their frequency in the systemic vessels. This divergence is not surprising. It is but a prolongation into the efferent vessels of the familiar contrast between the liability of the left heart to acquired disease and the immunity of the right heart from the same. The obverse contrast between the frequent incidence of ante-natal deformity of the right heart and its rarity in the left heart is not so plainly seen in the arterial parts of the two circulations. Yet the experiences recorded in this paper suggest that this contrast also holds good. We shall give some account of congenital anomalies of the pulmonary artery, together with examples of acquired disease of the same, in which hints of a congenital factor may be traced. In the first place, however, it may be well to give a brief account of earlier records of cases similar to those presented here.

Congenital Anomalies of the Pulmonary Artery.

Imperfect formation of the pulmonary artery, erroneously described as 'pulmonic stenosis', is the most familiar of all serious congenital anomalies of the heart. Scarcely less familiar, though much rarer, is that in which persistence of the ductus arteriosus leaves the pulmonary artery open to the reception of blood from the aorta. Far less familiar, but more closely related, perhaps, to the present subject, is a congenitally wide pulmonary artery, the recorded cases of which are few. The condition is regarded as secondary by most of the authorities. Rokitansky and Schwalbe (1) consider it to be the result of hypoplasia following imperfect development of the pulmonary bulbus, ostium, or trunk; or to be due to increased intrapulmonary arterial pressure, the result of patency of the ductus

[1] Received May 5, 1927.

arteriosus or of ventricular and septal defect. As a primary condition it is said by Maude Abbott (2) to be rare. Pfaundler and Schlossmann (3) record six cases, most, if not all, of these accompanying ventricular septal defect or persistent ductus; the case reports of their series are not detailed. In one case (4) in which the dilatation appeared to be primary, the cause was found to be an obliterating phlebitis of the pulmonary veins. In the first of the cases recorded here, it might be held that the artery became dilated as a result of pulmonary fibrosis resulting from congenital bronchiectasis (5). On the other hand, it seems improbable that a lesion which could not operate till the child was breathing would compel a dilatation of the pulmonary artery within a few weeks of birth; for the bruit which announced the presence of a pulmonary anomaly was noted when the child was five weeks old.

Of *acquired lesions of the pulmonary artery* there are many scattered records. In Posselt's (6) excellent summary of these are references to papers by Kinglake (7) and Kreysig (8) written over a hundred years ago, which appear to describe lesions similar to certain of these we are now about to record.

Sansom's (9) summary of the subject, written in 1896, is brief and to the point; Posselt's is anything but brief, but as it contains all the references down to 1908, it may be regarded as standardizing our knowledge to that point. His own experience of ten cases may be taken as typical of his treatment of the whole subject. Of these ten, there were three in which the arterial change was apparently primary, and seven in which it coincided with chronic valvular disease, particularly mitral stenosis. He brought forward some evidence to prove that the primary lesions are infective in origin, and endeavoured to show that pulmonary atheroma, whether primary or secondary, was responsible for a certain clinical picture.

This conception of pulmonary atheroma as a lesion susceptible of diagnosis during life was powerfully reinforced by papers from India on the one hand, and from South America on the other. Rogers's (10) article on primary pulmonary atheroma in Bengal, published in 1908, concludes as follows:

'(1) Extensive atheroma of the whole of the pulmonary arteries, with no marked disease of the systemic vessels, and without any valvular affection, is a not very rare cause of fatal cardiac dropsy in Bengal.

'(2) It produces extreme hypertrophy and dilatation of the right cavities, which may be so great that the right ventricle forms both the apex and the whole of the anterior surface of the organ; and as a consequence, clinically these cases have always been diagnosed as due to left-sided valvular disease, with the exception of one case recognized during life by the writer.

'(3) They occur nearly always between the ages of 20 and 40, and are almost certainly syphilitic in origin.

'(4) Palpitation, dyspnoea, and great dropsy due to tricuspid regurgitation are the principal symptoms, but they may be recovered from, for a time at least, under appropriate treatment. Death may occur in a fairly early stage from some severe strain, such as child-birth, but many of the fatalities result from a terminal

hydropericardium of insidious onset, and accompanied by dilatation of the coronary veins of the heart.'

About the same time Argentine physicians were describing under the heading of 'Cardiacos negros' a clinical picture slightly different from that of Rogers, yet, like that, referred to a basis of pulmonary atheroma. This has been called 'Ayerza's disease', after Abel Ayerza of Buenos Aires, and a good account of it is given by Arrillaga (11), whose conclusions are as follows:

'(1) There can be no doubt of the existence of the morbid entity which we have discussed under the name of "cardiacos negros", and which was described for the first time by Ayerza in 1901.

'(2) Its aetiological factors are chronic pulmonary disease processes, asthma, chronic bronchitis, tuberculosis, and pleural adhesion ; in short, all disturbances which have as their final result a state of pulmonary emphysema.

'(3) These processes evoke, in a pulmonary artery rendered sensitive by slow infections such as syphilis, paludism, &c., or by intoxications, a sclerotic process which causes a physiological stenosis of the arterial tract which the blood follows on its way to oxygenation.

'(4) The sclerosis of the pulmonary artery can be demonstrated not only microscopically and histologically in the specimens obtained from these patients, but may also be seen clinically in haemoptysis, cyanosis, dyspnoea, and hypercyanotic angina, from which these patients suffer.

'(5) They undergo an enormous hypertrophy of the right heart, involving both the auricle and the ventricle, which are forced to struggle against the obstacle in the peripheral circulation.

'(6) This hypertrophy, as well as the dilatation of the pulmonary artery in its early stages, can be clearly seen by radioscopy and radio-photography.

'(7) The principal symptoms of this entity are: cyanosis, hyperglobulia, dyspnoea, cough with mucous or muco-purulent expectoration, cephalalgia, hypercyanotic angina, haemoptysis, vertigo, an overpowering desire for sleep, &c.

'(8) Its course in the pulmonary stage is a very long one; after about twenty years as a pulmonary complaint it comes before the clinician in its cardiac phase.

'(9) The course of the "cardiaco negro" stage is also long, and varies from two to five years.

'(10) These patients may end up as "cardiacos negros" and die in their sleep, without having suffered from a trace of oedema, after showing the right gallop rhythm. Others, in whom degeneration of the cardiac fibre has taken place early, succumb to ordinary asystole, caused by failure of the right heart, and die in a state of advanced anasarca. Finally, some die of complications, of which the commonest is broncho-pneumonia.'

That some of these lesions are syphilitic was early suspected. Rogers, indeed, thought that all his cases were caused thus. Warthin (12), in 1917, showed very definitely, by demonstrating spirochaetes in the lesions, that—in some cases at all events—a syphilitic origin was undeniable. More recently

again, various writers have proved that in other cases no evidence of syphilis can be seen (Veale and Coombs (13), Mattirolo (14), Gamna (15)). One of the objects of this paper is to confirm the view that there is, on the one hand, a syphilitic, and on the other hand a non-syphilitic sclerosis of the pulmonary arteries. In connexion with the non-syphilitic cases the available evidence will be brought together in favour of an inherited aetiological factor, such as, we believe, was first suggested by Percy Kidd (16) in 1904.

Records of Cases.

Case I. R. B., born 25.4.21. Weight 6 lb. Seen at age of five weeks. Nutrition fair, no digestive symptoms, breast fed, no cyanosis, no respiratory symptoms or signs. A loud systolic murmur was audible over the pulmonary valve area. She was seen and examined every week. The bruit remained constant in position, though varying somewhat in intensity. She had numerous attacks of dyspnoea, and was sometimes cyanosed. At the age of seven weeks she had a bad attack of cyanosis. At four months she developed a cough and had a convulsion. No signs were found in the chest and pertussis was suspected. The cough persisted, varying in intensity, but no physical signs were noted till at the age of seven months, when a few rhonchi were audible. Dyspepsia and thrush were noted. At the age of eight months she was reported doing well, and her weight was 16 lb. Bruit still audible. Later, attacks of dyspnoea and cyanosis recurred frequently and the weight remained practically constant. At ten months she was admitted to hospital in an attack of broncho-pneumonia and died shortly afterwards.

Clinical diagnosis. Congenital pulmonary stenosis. Bronchitis.

Necropsy. Poorly nourished infant.

Heart. Globular in shape; right ventricle dilated and hypertrophied, containing some ante-mortem clot. Pulmonary valve perfectly competent. Pulmonary artery dilated immediately above the valve, the circumference being about twice that of the aorta. The dilatation was seen to be present throughout the course of the vessel and its branches. The vessel wall showed no degeneration in any part. Ductus arteriosus closed. Right auricle dilated. Left side of heart showed no abnormality and the septa no defects.

Lungs. A little haemorrhagic lymph present on both pleurae, chiefly posteriorly. Lungs nodular on palpation and on section showed purulent bronchitis and bronchiectasis, with peribronchial fibrosis (Plate 2, Fig. 1). One or two cysts, the contents unfortunately washed away, were visible. On section, these cysts were lined by well-formed bronchial epithelium and scanty islets of cartilage were found in their walls: some appeared to communicate with bronchi and others showed no connexion. The fibrosis was peribronchial and patchy, not extensive enough to be termed a cirrhosis, and large areas of lung showed no excess of fibrous tissue. The changes were similar in both lungs, and in both the lower parts were more abnormal than the upper.

The other viscera showed no changes of any importance beyond evidence of toxaemia and signs of circulatory failure, mainly terminal.

Case II. J. A. P., born 2.5.22. Weight $8\frac{1}{2}$ lb. at birth. Two other children, one older and one younger, were perfectly healthy. The younger one was then three years old and had been carefully watched. Seen at age of nine weeks, for marasmus with vomiting. Child breast fed. A loud systolic bruit was audible all over the praecordium, loudest at the apex. This remained constant in position and intensity at examinations made once a week. His mother stated that when five months old the child looked blue around the mouth, but cyanosis was never

observed. The weight fluctuated between 6 lb. 4 oz. and 7 lb. 3 oz. At the age of six months the child suddenly became ill with no tangible symptoms, was brought to hospital, and died within a short time of admission.

Diagnosis. Congenital heart disease. Heart bulbous in shape. Hypertrophy of right side with some dilatation, especially of right auricle. The trunk of the pulmonary artery was distended, and this dilatation could be seen to occur throughout the course of the artery in the lungs. Valves showed no abnormality. Foramen ovale patent but well guarded. A defect of 6·5 mm. diameter was present in the usual site—the unguarded space of the ventricular septum. The ductus was closed. Apart from the distension the pulmonary artery showed no abnormality in any of its coats.

Lungs. There was some congestion; apart from the dilatation of all the radicles of the pulmonary artery there was no other change. The remaining viscera showed the signs of circulatory failure.

Case III. On May 21, 1913, N. S., a well-developed little girl, aged 5 years, was brought to the Bristol General Hospital by her mother, who said that ever since an attack of bronchitis eighteen months before she had been increasingly disabled by shortness of breath. No history of any other illness was forthcoming. There was nothing in the family history to hint even faintly at a syphilitic factor. The child was very blue, and obviously dyspnoeic. The fingers were not actually clubbed, but the nails were abnormally curved and the tips were shiny. No oedema was noted. The pulse was regular. Examination of the chest showed that the heart was enlarged to the left, the apex beat, which was wide and feeble, lying in the fourth left interspace a little way beyond the left mammary line. At this time no distinct enlargement to the right was made out. At, and external to, the point of maximum impulse a long, but not loud, systolic murmur was heard, and the pulmonic second sound was doubled. Neither at this time nor subsequently was any bruit heard at the base of the heart, though it was carefully looked for several times. At the bases of both lungs there were many alveolar râles, but the percussion note was not impaired. The urine at this time contained a trace of albumin. The liver was palpably enlarged, but not the spleen. After a stay of only one week she was taken home by her parents. The bronchitic signs were much less pronounced, but they had not disappeared.

In March, 1914, she was once more admitted. The most striking feature, apart from the dyspnoea and cyanosis, which were much more pronounced than on her last visit, was the supervention of oedema of the face, feet, and ankles; her face was so puffy that it seemed impossible to believe that she was not suffering from Bright's disease; however, there was only the smallest trace of albumin in the urine and no casts, though there were a few pus cells and many bacilli. The total daily output was small. There was a good deal of cough with expectoration of thick phlegm, which however had no offensive smell. The fingers were no more clubbed than at her last visit. An examination of the chest discovered bronchitic signs much like those observed previously. The point of maximum cardiac impulse lay in the fifth left interspace, about one finger's breadth outside the nipple line; it was diffuse and not powerful. During expiration pulsation was palpable at the pulmonic area. A faint pulsatile movement could also be felt to the right of the sternum. At, and external to, the point of maximum impulse a late systolic thrill was felt, and in the same area a long, definite, but not very loud bruit was heard, beginning late in systole and running up to and perhaps into the second sound. This bruit was conducted into the back by way of the left axilla, and was distinctly heard at the inferior angle of the left scapula. The pulmonic second sound was accentuated, but no murmur was heard at the base, or in the supraspinous fossae behind, or in the neck. The cardiac dullness extended from the left anterior axillary line to a finger's breadth

to the right of the sternum; upwards it reached to the inner end of the second left interspace. A skiagram showed that the cardiac volume was increased to the right of the sternum, and also upwards to the left.

On admission there was reason to think that she had improved, for the bronchitic signs had disappeared and the oedema was very much less, but she was very listless and sleepy, and within two days after admission she died rather suddenly.

Necropsy. On opening the chest the heart was found to be considerably enlarged, owing to the dilatation of the right ventricle, which had come to occupy the whole anterior surface of the heart. On opening the heart the chamber of the left ventricle was found to be exceedingly small; the muscle wall was of good colour and fairly firm, and measured 1 cm. in thickness. The left auricle was similarly of small size with thickened walls.

The cavity of the right ventricle was greatly dilated (holding approximately 4 oz.), with considerable hypertrophy of the moderator band and all the papillary muscles, which also showed fibrous thickening of the subendothelial tissues. The right auricular cavity was dilated, the wall measuring 5 mm. in thickness.

The foramen ovale was closed except for a pin-point orifice at the inferior border. There was no opening in the undefended space of the septum, and the ductus arteriosus was represented by a fibrous cord only. The mitral opening was normal in size: its aortic cusp showed some atheromatous patches, particularly on its ventricular aspect, and the vessels at the root of the valve flaps were congested. The aortic orifice admitted the little finger; the valve segments were somewhat clouded and thick, and had small spots of atheroma at the junctions of the lunules, whilst some recent atheroma was seen along the margins of the pockets, and at the insertion of the cusps into the root of the aorta. The tricuspid valve admitted two fingers, its margins were firm and thickened, and the endothelium on the surface of the valves was transformed into a dense white membrane with subendothelial nodosities here and there.

The pulmonary orifice measured 15 mm. in diameter; the valve segments showed no sign of disease. In the descending aorta were long streaks of atheroma along its length, particularly surrounding the orifices of its branches. The pulmonary artery and its branches were the seat of a very pronounced nodose atheroma.

Microscopically the atheromatous patches showed great thickening and multiplication by lamination of the tunica intima; the internal elastic tissues and loose subendothelial elastic fibres were replaced by a highly cellular loose areolar tissue, the cells being round cells with a reticular nucleus and a nucleolus. Very few fibroblasts were to be seen. Beneath this cellular layer there was a well-organized tissue composed of fibres loosely arranged, but in two or three patches aggregated into a dense nodule resembling a scar. There was no cellular infiltration of the deep elastic layer until the line of demarcation between that layer and the muscle tissue was reached, when an obvious round-celled infiltration was observed. The capillaries in the muscle layer showed a marked endothelial proliferation, as did those within the elastic layer. There was no evidence of gummata, nor were any treponemata to be found in sections stained with silver.

The muscle of the ventricle and auricle appeared normal; there was no infiltration of the connective tissue or any focal areas of cellular aggregation, and the blood-vessel walls showed no sign of any disease. There was no evidence of disease in the mediastinal glands.

Case IIIa. I. S., born April, 1920. (Sister of above patient.) Two months later it was noticed that her heart beat fast after crying. There was no asphyxia at birth, and no chest infections until March, 1924, when she recovered from a slight attack of influenzal broncho-pneumonia. Her symptoms were: cyanosis and dyspnoea, worse on exertion; first noticed definitely at the age of 2. There were no physical signs of cardiac enlargement in either direction, though with

the X-ray screen some right heart enlargement was perceptible. There was a systolic murmur at all areas, louder over the lower half of the praecordium. At the pulmonic area there was a very loud second sound, louder when she lay down, and at the same area pulsation forcible enough to remind one of an aneurism was felt. Pulsation could also be felt beneath and to either side of the sternum. Red blood-corpuscles 4,600,000 per c.mm. Wassermann reaction negative. The electrocardiogram (for which we are indebted to Dr. C. E. K. Herapath) showed right ventricular preponderance.

This child had been watched for about four years. The physical signs had not altered, but the symptoms had become a little worse. The family tree of Cases III and IIIa is shown below.

Family Tree of Cases III and IIIa.

F.'s F. d. 72. = F.'s M. d. 72. — M.'s F. alive. = M.'s M. d. 46, pleurisy.

Father, at 47, died of heart disease, probably rheumatic. — Mother 42, heart normal.

Boy	Girl	Girl	Girl	Boy
22, living.	d. $3\frac{1}{2}$ of broncho-pneumonia.	d. $1\frac{1}{2}$. Found dead in bed, after bronchitis.	d. $5\frac{1}{2}$. Case III.	14, living.
Girl	Girl	Boy	Girl	Boy
$11\frac{1}{2}$, living. Examined, nothing abnormal found.	9, heart normal.	1 yr. 8 mths., drowned.	6. Case IIIa.	d. 8 mths. of bronchitis.

Case IV. Primary arteriosclerosis of intrapulmonary branches of both pulmonary arteries.

Clinical Abstract. A deeply cyanosed woman of 22 was admitted to the General Hospital, Bristol, for swelling of the legs and dyspnoea, having been seriously incapacitated for the previous five and a half months by dyspnoea and palpitation.

History. She had suffered from breathlessness on exertion and nocturnal dyspnoea from the age of 6, the onset coinciding with an attack of scarlet fever. No other significant facts in history or antecedents. No history of rheumatism or chorea. For the last five and a half months she had been confined to bed most of the time, including a six weeks' stay in hospital three months before, when she was admitted for swelling of the legs, ascites, and orthopnoea. She was then found to have considerable oedema of the lower limbs, lumbar region, and chest wall; the liver reached two inches below the costal margin, and eight pints of ascitic fluid having the characters of a mechanical transudate were withdrawn.

During her stay in hospital she was strikingly cyanosed, and her colour hardly improved, but her pulse was always recorded as being regular in force and frequency. Beyond a persistent increase in cardiac dullness to the right, no definite signs were found in the heart. For the first few nights after admission she had alarming orthopnoea and was delirious; her urine was scanty, high coloured, and albuminous, and she was intolerant of digitalis by the mouth. As her urinary secretion became re-established she improved sufficiently in six weeks to be discharged, but was readmitted two months later for an acute exacerbation

of all her symptoms, and died a month later. During this month the oedema, orthopnoea, and oliguria hardly responded to treatment. The oedema extended to the forearms and hands; the pulse frequently reached 136, but its regularity was maintained. No alteration could be detected in the heart sounds sufficiently definite to diagnose a valvular lesion, but the cyanosis was intense enough to raise the question of a congenital defect.

This cyanosis, coupled with a regular pulse and extensive oedema, constituted a clinical picture very similar to that which had already been seen in Case V, and she was diagnosed as probably suffering from pulmonary arteriosclerosis; the Wassermann reaction being negative, and no signs of healed or active syphilis detected, this was thought to be non-syphilitic.

Post-mortem Examination.

Externally. Considerable oedema of lower limbs, lumbar region, chest wall, forearms, and hands; striking cyanosis of face.

Thorax. Dense universal pleural adhesions inseparable at bases, involving visceral pericardium on left side. Slight excess of fluid in otherwise normal pericardial sac.

Lungs. Rather shrunken, somewhat deformed and leathery, except at bases where they were oedematous and rather friable. Pleurae thickened and torn, and surface moderately fissured. Middle lobe on right side, and tissues about lung root on both sides, felt fibrous and dense, but towards outer surfaces this was less marked. Main branch of pulmonary artery stood out prominently at the root; its thickened walls showed many yellow, subintimal plaques, streaks, and blotches. These were more numerous and closely set in the branches, and in those of the fourth and fifth dimension were striking. The changes were diffused throughout both lungs. A few small terminal infarcts were present in each.

Heart. Externally—showed a striking increase in size: globular in shape. Right heart occupied the whole anterior surface, formed the apex, and appeared to constitute quite two-thirds of the heart's bulk (Plate 2, Fig. 2).

	Right Heart.	Left Heart.
Cavities	Greatly dilated	Normal
Valves	Tricuspid – normal Pulmonary – normal	Mitral—slightly rolled edge but no other change Aortic – normal
Myocardium	Hard and rigid Cuts with resistance Brownish red	Soft and flabby and much less resistant Pale yellowish brown
Thickness of ventricular wall at apex	11 mm. (normal 2·5 to 3 mm.). Auricular walls proportionately increased in thickness	9 mm. (normal 9 to 12 mm.)
Circumference of orifices	Pulmonary 7·1 cm. (normal 8·5 to 9 cm.)	Aortic 5·5 cm. (normal 7·7 to 8 cm.)
Coronary vessels	Large; prominent but not sclerotic	Normal

The bulk of muscle on the right side was thus about four times the normal, and the normal ratio between the circumference of the pulmonary to the aortic orifice had increased from 1·1 to 1·3. Histologically the myocardium of both ventricles showed some hypertrophy of fibres, with inconspicuous and scattered fatty change, but no inflammatory reaction or fibrosis. The thoracic and abdominal aorta showed no noteworthy change. There was no abnormality in the vessels of the liver or kidney.

The pulmonary artery and main branches were considerably thickened and more rigid than normal, but no naked-eye lesions were seen on the intimal surface until the lung roots were reached. The thickening of the wall of the main vessels may be judged from the following measurements, to obtain which a strip of the vessel 3 cm. wide and 1 cm. long was cut from the anterior wall of the main vessel just above the valve curtains:

	Average Thickness.	Maximum.	Minimum.
Case described	2·2 mm.	2·4 mm.	1·8 mm.
Four cases of cardiac hypertrophy from chronic renal disease	0·75 mm.	0·85 mm.	0·6 mm.
Three cases of mitral disease without naked-eye pulmonary arteriosclerosis	1·15 mm.	1·3 mm.	0·95 mm.
One case of mitral disease with marked pulmonary arterio-sclerosis	2·1 mm.	2·4 mm.	1·8 mm.

Histopathology.

Pulmonary arteries. All branches of the pulmonary arteries except its arterioles showed nodular subintimal thickening, equally distributed through each lung. This was definite but not striking in the main branch to each lung, but it was well marked in all vessels ranging from 7 to 2·5 mm. in diameter, being most prominent in those of about 4 mm. diameter. Combined with this change was another, no less striking when longitudinal sections are taken, stained by orcein, and compared with normal controls. This affected the larger vessels, the main stem, its two branches, and the large elastic vessels in the roots, and consisted of a uniform general increase in thickness of the vessel walls due to increase in their elastic tissue, with a less pronounced degradation of their elastic fibres, and replacement-fibrosis (see Plates 3 and 4, Figs. 3, 5, and 6). There was no evidence of any inflammatory process.

Main vessel and large branches. The thickening in these vessels was entirely due to increase in their elastic tissue. A strong compact band of closely applied elastic laminae, seen best in longitudinal section, accounted for much of the thickening, forming as it did a layer much thicker than is seen in the normal vessel. Some of the thickening was due to slight general swelling of the elastic fibres in the outer half of the media, where the elastic elements were widely separated from each other, presumably by fluid. As the lung roots were approached the intima began to show slight and irregular thickening of nodular distribution.

Intrapulmonary branches. In the larger vessels and those down to 4 mm. in diameter nodular thickening of the intima was well marked. Between the nodules the thickened and presumably hypertrophied subintimal elastic layer was very prominent. As the nodule of thickened intima was approached the closely set fibres of this layer separated, frayed out, and became indistinct; and, although this could not be clearly demonstrated, several sections strongly suggested that the nodular thickenings in the intima were actually composed of the swollen degenerate subintimal band of elastic tissue which formed such a clear compact layer in the main vessel. In smaller vessels this layer was replaced by a thick, bold, internal elastic lamina which ceased abruptly at the margin of each plaque. The intimal plaques themselves were almost acellular. In their central parts there were usually a moderate number of lipoid clefts in the fibrillated tissue, and scanty lipoid phagocytes with foamy cytoplasm in close relation to them. There was no calcareous deposit.

Abdomen. Much clear fluid filled the flanks. The spleen, although not noticeably increased in bulk, had the appearance and consistence of the spleen of chronic venous congestion of long standing. The liver was enlarged to the level

of the umbilicus in the mid-sternal line, was deep brownish red, and on section showed the typical appearance of chronic venous congestion with much fatty degeneration. Microscopically this was confirmed, and a moderate degree of centro-lobular necrosis found. The kidney had the typical naked-eye characters of chronic venous congestion.

The lungs showed the microscopic changes associated with chronic venous congestion of the degree found in chronic mitral disease, but there was more fibrosis and a more obvious concentration of the fibrosis at the lung root than such cases show. At a distance from the root this change was not conspicuous; whilst in the root, and spreading from it, there was a wide-meshed network of fibrous tissue which appeared to originate in the connective tissue around the vessels. The bronchi showed widespread and severe acute catarrhal inflammation with much disorganization of their walls from recent inflammatory swelling, but no clear evidence of chronic disease.

Summary of post-mortem examination. 1. Widespread non-syphilitic sclerosis of the intrapulmonary branches of both pulmonary arteries, most marked in vessels of 5 to 3 mm. in diameter, affecting all branches down to 1 mm. in diameter, but sparing the arterioles, unassociated with generalized blood-vessel disease, valvular or congenital cardiac disease, and of greater intensity than in the average case of fatal mitral stenosis.

2. Chronic interstitial fibrosis of both lungs equal on both sides and without gross deformity, more marked at the roots than towards the surface and originating in the periarterial connective tissue.

3. Hypertrophy and dilatation of the right heart, dilatation of the pulmonary orifice.

4. Chronic venous congestion of viscera and widespread dropsy.

Case V. Syphilitic arteritis of pulmonary arteries and all main branches; widespread obliterating endarteritis of pulmonary arterioles; gross perivascular fibrosis of both lungs; generalized syphilitic arteritis.

Clinical abstract. A woman of 39 was admitted to the General Hospital, Bristol, moribund, and died thirty-six hours later. The history showed that for three years she had been short of breath with a slight cough. During the past winter these symptoms had been aggravated; the cough was loose, there was abundance of purulent sputum, and nocturnal orthopnoea. For a fortnight before admission there had been oedema of legs, scanty excretion of urine, and continual orthopnoea.

On admission. Striking cyanosis recalling that of congenital heart disease. Great orthopnoea, out of all proportion to other symptoms. Pulse 100, and quite regular in force and frequency. Much oedema of lower extremities. Dullness at base of both lungs. Blood-pressure: systolic 120, diastolic 75. Faint diastolic murmur in pulmonary area. Knee-jerks absent, and pupils fixed to light. Wassermann reaction in cerebro-spinal fluid strongly positive.

On admission she displayed a striking degree of cyanosis, rarely seen even in advanced mitral stenosis. The orthopnoea was equally remarkable. The pulse-rate was 100 per minute, and its rhythm regular. The systolic blood-pressure was 120 mm. Hg, the diastolic 75. The lower limbs were very swollen, and the bases of both lungs were dull. A diastolic murmur was faintly audible in the pulmonary area.

The knee-jerks were absent, and the pupils did not react to light. A Wassermann test of the cerebro-spinal fluid yielded a strongly positive result.

Post-mortem Examination.

Externally. Oedema of both lower limbs, slightly of lumbar region. Striking cyanosis. Several oval 'tissue-paper' scars over both shins.

Lungs. Irregular in shape, considerably deformed and deeply scarred by extensive fibrosis spreading fan-wise into each lung from its root. Apices and outer borders oedematous. The lower lobes especially were airless, leathery, tough, and inelastic. The pleural surface was scored by deep linear clefts and the pleura was thick and opaque. On section a grey close-meshed network of fibrous tissue ramified through the whole lung, sparing only the anterior part of each upper lobe. Groups of distended alveoli alternated with areas of fibrosis and collapse. The branches of the pulmonary artery stood out very prominently and showed many small yellow subintimal patches of thickening, clearly seen in all branches down to those just visible to naked eye. The main pulmonary artery showed only slight patchy sclerosis, but the change was marked almost immediately after its division into its two main branches. From naked-eye examination, the sclerosis appeared to be most marked, the plaques thicker and more closely set, in arteries from 2 to 8 mm. in diameter.

Heart. Considerably enlarged. Weight (free of clot) 17 oz. The enlargement affected both sides, but chiefly the right, and the left side was dislocated backwards. No valvular disease found and no gross myocardial changes. The hypertrophy of the right side had produced an average increase in thickness of muscle in both chambers to 2·5 times the normal: that of the left side an increase to 1·6 times the normal.

Thoracic aorta. Although the cusps of the aortic valve were spared, the aorta showed the typical linear scarring of syphilitic aortitis, to which were added much gross atheromatous change, pouching in the ascending arch, calcification and brittleness in its transverse portion. Appearances characteristic of syphilitic infection were present in the abdominal aorta.

Abdominal organs. The liver was enlarged from chronic venous congestion and fatty changes, and sections were typical of long-standing venous stasis. The spleen was small (long axis 8·5 cm.), indurated, and congested; the kidneys showed chronic congestion but no primary disease.

Histopathology.

Aorta. Showed the typical changes of advanced gummatous infiltration with superadded and moderate atheroma.

Pulmonary artery. Main trunk. The vasa vasorum showed endarteritis of the type associated with syphilis, and perivascular lymphocytic infiltration spreading into and destroying the elastic tissue of the media at many points. Lying between the media and adventitia in one section was a focal lesion showing the histological details of an early gumma. A few foci of calcification were found at the junction of the media with the greatly thickened intima, but all changes seemed to be much more recent than the changes in the aortic wall and those in the intrapulmonary vessels.

Vessels in the lung root. Irregular and considerable subintimal thickening was seen along the whole inner circumference of the first branches of each pulmonary artery in the root, and with this change diffuse lymphocytic infiltration and much disorganization and destruction of the media. (See Plates 3 and 5, Figs. 4 and 7.) In one vessel the lumen was reduced by about one-fifth by a mass of organizing thrombus, but the other branches showed an intact intima. The subintimal plaques were much more cellular than in the main vessel and spindle-shaped fibroblasts were numerous. The adventitial lesions were more diffuse and less well defined. No calcification was found.

Intrapulmonary branches. Large—diameter 4–6 mm.—showed changes of equal severity to those found in vessels at root. The vessels lay in a thick cuff of fibro-cellular tissue. The subintimal plaques were more irregular and very cellular. *Small*—diameter under 2 mm.—lumen greatly narrowed by proliferation of the intimal endothelium. The vessels lay in broad fibrous tissue trabe-

culae which ramified through the whole lung, and had a constant relation to its vessels. In the arterioles the reduction in lumen was extreme and many were occluded by organizing thrombi. (See Plate 5, Fig. 8, *a*, *b*, and *c*.)

Lungs. Broad fibrous tissue bands traversed the lung in all directions. They originated in the dense fibrous tissue investment found around the medium-sized arteries and formed an irregular and wide-meshed network.

Although there was a moderate degree of peribronchial fibrosis no constant relation could be made out between this and the general cirrhosis. The perivascular fibrosis was marked and gross at the roots, and large groups of alveoli were isolated. Towards the surface the fibrosis was finer. No localized intrapulmonary lesions resembling gummata were found. The alveoli were distended and irregular, frequently with ruptured walls. There were several foci of recent consolidation throughout both lungs, and usually where this was absent and the alveolar walls preserved there was a copious intra-alveolar exudate of albuminous fluid and desquamated cells. The bronchi showed widespread catarrhal inflammation and less recent subepithelial inflammatory changes, apparently resulting entirely from surface infection following retention of secretion.

Spinal cord (cervical). Sections stained by Pal-Weigert method showed symmetrical degeneration in the posterior columns, typical of the lesions of tabes dorsalis.

1. *Summary of post-mortem examination.* Long-standing syphilitic mesaortitis with superadded atheromatous changes.
2. More recent gummatous infiltration of the pulmonary artery and its main branches.
3. Widespread obliterating endarteritis of the pulmonary arterioles.
4. Gross perivascular fibrosis of both lungs.
5. Early sclerosis of the posterior columns of the spinal cord.
6. Chronic venous congestion of viscera.
7. Acute right-sided cardiac dilatation and generalized dropsy.

Comments.

Aetiological. It is difficult to separate from each other the various causal factors that may be held responsible for progressive deterioration of the systemic vessels. Examination of the arteries of the lesser circuit, however, quite clearly brings out the harmful influence of several agencies. In the first place, there is an obvious developmental factor in Case II of our series. Dilatation of the pulmonary artery was associated with a septal defect, and it can therefore hardly be doubted that its origin lay in interference with the intracardiac pressures arising early in antenatal life, or at all events in something inherent in the cardiovascular tissues and not imposed on them from without.

In Case I there is another possible factor; or rather there is a possible reason, more plausible than in most developmental faults, furnished by the condition of the lungs. Intra-uterine fibrosis of the lungs, narrowing the capillary field, might reasonably be held to heighten the pressure within the pulmonary artery during the first few hours of separate existence to such a pitch as to cause a permanent widening of the artery. As a general principle these mechanical explanations of morbid processes are open to suspicion; but in this instance it is difficult to furnish an alternative explanation of the coincidence of pulmonary fibrosis with enlargement of the pulmonary artery, except to say that it is an

example of the association of malformations. It is true that a consideration of Case V, in which acquired syphilis has caused both fibrosis of the lungs and disease of their arteries, suggests the possibility of some infective causation. But if any infection had been responsible for the changes in Case I, it must have burnt out long before death, for the pulmonary artery did not show any trace of inflammatory reaction.

Case III shows a very definite familial influence. One sister is known to have died of a cardiac failure, which apparently arose out of degenerative changes in the pulmonary artery. Another sister, now about the same age as this one had reached at the time of death, presents closely similar physical signs and symptoms. This child was shown at the Bristol meeting of the Association of Physicians, and it was agreed by those who saw her that her signs and symptoms pointed unmistakably to some lesion of the pulmonary artery, so that we feel justified in claiming that this is an example of pulmonary disease showing a familial incidence.

In what does the familial influence lie? Certainly not in any syphilitic taint; for we could find no evidence of syphilis in the lesions of the child who died, nor in the sister who has been so long under observation, nor in those other members of the family whom we have examined. The fact that the mother presents the same violaceous colour of the cheeks as her daughter suggested to Dr. Parkes Weber, at the meeting just spoken of, the possibility of a familial hypercholesterinaemia, but we have not found it possible to work out this hint. The father had a chronic cardiac lesion, predominantly mitral and apparently conforming to the usual rheumatic type. He died recently, but no autopsy could be arranged. It is possible, of course, that there was in his case some unsuspected aetiological factor, but if so it was at all events something which had fastened on the left heart and not on the lesser circulation. It appears that there is some inherited influence at work in the persons of this family, the nature of which is entirely hidden from us.

Case IV is also puzzling. It is tempting to assume, with Rogers, that all such lesions are syphilitic in origin, particularly since it has been proved in many instances, as in Case V and in Warthin's cases, that there is an acquired syphilitic lesion of the pulmonary arteries. But in our Case IV neither during life nor after death was there any evidence of syphilis discernible, not the slightest hint of mesaortitis being found. And there are others, similar to this one, in the literature that are clearly different in their morbid histology from the arterial lesions of syphilis. As in our Case IV, these patients have been young adults, women as often as men, and it is very unlikely that the infection of syphilis would achieve a serious injury of the pulmonary artery within so brief an interval after the primary infection, or with a sex incidence so different from that of syphilitic aortitis. Neither do we feel attracted towards the view that in patients of so early an age the exciting cause must be inherited syphilis. If this were so, the most likely of all recorded cases to be syphilitic would be our Case III, because occurring in the youngest patient; but, as we have already shown, it is

as certain as anything in clinical medicine can be that in this patient's case there is nothing in favour of the syphilitic hypothesis.

That there is some other causal agent to be invoked in many cases is suggested by the relatively frequent occurrence of degenerative lesions of the pulmonary artery in India (Rogers) and in South America (Arrillaga, and others). What that may be it is impossible to surmise. The fact that geography has an influence might be brought forward as support for an infective hypothesis. On the other hand, it might be explained on the grounds of racial predisposition, laying the blame for the lesions on the soil rather than on any special seed of disease. If there were any infective element in Case IV it must have played a very subordinate part.

In Case V the syphilitic nature of the lesion was beyond doubt. Its close similarity to syphilitic disease of the aorta, which was itself the seat of a syphilitic lesion, its association with a coarsely trabecular fibrosis of the lung, and—even more striking—with the symptoms and post-mortem changes of an early parasyphilitic lesion of the cerebro-spinal axis, cannot be explained otherwise.

What is not quite so easy to understand is the nature of the relation between the arterial changes and those in the substance of the lung. Did either of these phenomena precede and pave the way for the other, or are they simultaneous results of one parent process? Alongside of this question may be set that other, which we have already asked, as to the nature of the link between widening of the pulmonary artery and congenital bronchiectasis in Case I. In many of the recorded cases of pulmonary atheroma the symptoms that have been most prominent when the patient first came under observation have already been those of diffuse bronchitis. Arrillaga, indeed, believes that in all his cases of 'cardiaco negro' the circulatory disease was preceded by some years of progressive pulmonary disease. In Case IIIa, however, the child has been watched for several years, and had only once or twice developed a bronchitis that could be detected; and in each attack the course has not differed from that of a febrile catarrh of the bronchial tubes such as may be seen in any child. In the record of the syphilitic cases, also, there is an absence of any mention of changes in the lungs like those seen in our fifth case. It is clear, therefore, that infective lesions of the lungs are not essential to the development of the arterial changes that we have reported, whether in the syphilitic or in the non-syphilitic cases.

It is possible to produce evidence of injury to pulmonary arterioles by infections; on the one hand borne thither by the systemic blood current, on the other hand apparently attacking the tissue of the lung first and its arterioles later. As an instance of the former may be quoted that intimal proliferation within the smallest arterioles of the lungs sometimes seen in animals experimentally inoculated with streptococci from cases of rheumatic infection (17); while an example of the latter is furnished by the arterial lesions observed by Mocaigne and Nicaud (18) and others in connexion with pulmonary aspergillosis. These fragmentary data may serve to provoke further inquiry into the state of the pulmonary arteries in various infections, but they are not weighty

enough to enter into a summing up of the arguments for and against the recognition of an infective factor in the cases recorded here. Of these, our view is that in Case V the infective factor is all-important, while in the remainder a congenital or inherent factor is discernible to a degree varying inversely as the age of the patient.

We have not been able to satisfy ourselves that mechanical stress has been the primary factor in any of our cases. This factor may, and probably does, account for the arterial degeneration of mitral stenosis, and, as Arrillaga claims, is likely to be the determining factor in the production of the 'cardiaco negro' who for years has had pulmonary emphysema. The histology of the arterial lesions in Case IV of primary pulmonary arteriosclerosis suggests that the vessels of the lesser circuit were fighting against, and were eventually overcome by, a raised internal pressure. This view is supported both by the elastic hypertrophy of the walls of the large vessels and by the elastic degeneration in those of the smaller. We are, however, left without any adequate explanation either of the increase of pressure, or of the supersession of hypertrophy by degeneration at so early an age. Possibly the moderate intrapulmonary fibrosis seen in this case may be held to furnish an explanation of the heightened pressure; while, as there was apparently no infective or toxic change to account for the early arterial degeneration, we may be allowed to claim this also as evidence in favour of an 'inherent' liability to degeneration more marked in the pulmonary than in the systemic arteries.

Briefly, our case for this belief in the importance of an inborn factor may here be summarized as follows. In the published records of sclerotic disease of the pulmonary artery four quite definite groups are discernible. In the first place, mitral stenosis and other lesions which throw an obvious mechanical strain on the pulmonary artery are often complicated by degenerative changes in that vessel and its branches. Secondly, as in Arrillaga's cases, these changes develop apparently as a consequence of chronic bronchitis and similar diseases of the lungs. The link between the two is possibly mechanical, possibly toxic, perhaps both mechanical and toxic. Thirdly, there are such cases as the fifth in our series, in which the arterial changes were indubitably syphilitic. Finally, there are cases such as that of our fourth patient: young adults whose pulmonary arteries degenerate without any obvious reason, mechanical or infective. These we explain in the light of our Case III as being the outcome of some familial or at all events inborn imperfection of the material of which the pulmonary artery is formed; with the more confidence because in these young subjects there is no direct evidence either of mechanical stress or of any toxic influence.

Morbid physiology. In the cases recorded here, as well as in those of other writers, there have been three prominent evidences of circulatory failure: dilatation with hypertrophy of the right heart, cyanosis, and dropsy. This last is only a late symptom, but is apt to be so diffuse, when it does appear, as to suggest a toxic or privational causation rather than one due directly to mechanical break-down of the circulation.

The others, however, are early, constant, and extreme. It is safe to say that in no other acquired disease of the heart or lungs does the right heart become so large as in these cases. In Case IV, as in several others recorded, the wall of the right ventricle was actually thicker than that of the left. It is easy enough to see why a disease that destroys the elasticity of the pulmonary arteries should demand hypertrophy of the right heart. Romberg, indeed, ascribed the hypertrophy to obstruction of the pulmonary circuit by narrowing of the arterial lumen; possibly this is partly responsible, but it appears unlikely to account for the whole or even for the greater part of the hypertrophy. We are disposed to lay the blame for the overwork of the right ventricle that is implied in the development of hypertrophy on the loss of elasticity in the pulmonary arteries. The fact that the right ventricle was hypertrophied in the syphilitic as well as in the non-syphilitic case is worthy of note. The relation of this loss of arterial resilience to extreme cyanosis is most interesting and suggestive. It seems possible that this simple yet striking fact may well prove to be the key to a better understanding of the origin of cyanosis.

At first we were tempted to suppose that in pulmonary atheroma there was such obstruction to the passage of blood through the lungs that oxygen saturation would be hindered. Yet slow passage through the lungs should mean a thorough contact and therefore saturation with oxygen. We venture to suggest that, just as cardiac oedema is usually due to loss of *vis a tergo* in the greater circuit, so also cardiac cyanosis may be due to similar failure in the lesser circuit.

The conclusion that retarded circulation would lead to more complete aeration of the blood is dependent upon the older theory that oxygenation of the blood is due simply to osmosis. By this theory, in pulmonary sclerosis the blood should be fully saturated with oxygen. But the reverse is found; cyanosis is one of the most prominent symptoms, and, indeed, orients the diagnosis.

The oxygen secretion theory of Bohr, supported by Haldane and others, furnishes an explanation, especially if it is read in conjunction with the experiments of Underhill (19). This observer tied the pulmonary artery and then released it, a procedure calculated to damage the parenchyma. After this, complete oxygen saturation does not result except on forced ventilation, a fact that does not accord with the osmotic theory. On the other hand, it is explicable if we attribute to the lung parenchyma the faculty of secreting oxygen. At all events, in pulmonary sclerosis we have a state of affairs analogous to that of Underhill's experiment. It is a diminution of the onward drive rather than an increase of the pressure in front that interferes with oxygen saturation, both in the experiment and in the disease. All that we wish to do here, however, is to commend to the notice of those who are studying the origins of cyanosis the fact that in our experience the deepest cyanosis we have observed in acquired cardiovascular disease is associated with lesions destroying the elasticity of the pulmonary arteries.

Symptoms. A definite clinical picture has been associated with primary sclerosis of the pulmonary artery by more than one writer. The very term

'cardiaco negro' used by the South American clinicians bears witness to this. So also does the fact that in one of our cases (Case IV) the diagnosis was made during life and confirmed post mortem. The same is true of one of Rogers's cases.

In another case recently seen the same diagnosis was offered, but no autopsy was allowed. The patient, a schoolmistress, 41 years old and single, was one of a large family, all surviving. At 25 she began to be dyspnoeic, and had to give up work. The dyspnoea was constant, with periodic exacerbations. She was always cyanosed. Recently the ankles had been dropsical, and during the past ten or twelve days she had had several epileptiform attacks. When seen she was unconscious, but apart from this there was no sign of nervous disease. The face, neck, and hands exhibited a deep plum-coloured cyanosis. The fingers were not clubbed. The pulse-rate was 140 per minute and its rhythm regular. The blood-pressure was 150 mm. Hg systolic, 85 diastolic. The lungs were somewhat emphysematous and there were a few moist sounds, but expiration was not greatly prolonged. There was a little dullness at the left base behind. The area of cardiac pulsation extended well into the left axilla, but the maximal point was only just outside the left mammary line, and the heart beat strongly in the epigastrium. There was a rather loud second sound at the pulmonic area and an occasional triple rhythm over the left upper chest. The patient died a day or two later. Although further investigation was prevented, we have described the clinical picture because it illustrates so clearly the grounds on which to base a diagnosis of sclerosis of the pulmonary artery; deep cyanosis coming on at an age which precludes a diagnosis of congenital anomaly, without physical signs of pulmonary or cardiac disease severe enough to account for the cyanosis. The diagnosis is strongly supported if signs of right ventricular hypertrophy are discernible. Other clinical features on which we remark are the protruding eyes, the absence of clubbed fingers, and the pulmonary diastolic murmur noted in our Case V. The polyglobulism in some cases has been so high that some writers think this arterial lesion is one cause of the Osler-Vaquez syndrome. Dropsy develops late, but is then apt to increase rapidly and to be general. Arrillaga remarks on the somnolent condition of his patients, and this was noted in the case just related as well as in our Case III.

Posselt went so far as to say that it was possible to recognize from the symptoms the presence of pulmonary arteriosclerosis as a complication of mitral stenosis and other forms of cardiac disease. We believe that there may be some relation between the depth of the cyanosis and the state of the pulmonary arteries in mitral disease, but our observations on this point are too fragmentary to justify any positive statement.

Treatment. It is obvious that the opportunity for relieving patients exhibiting the syndrome which we have described must necessarily be limited to treatment of symptoms in a majority of instances. It is, however, possible that early diagnosis in such a case as our No. V might have enabled us to institute anti-syphilitic treatment at a stage at which it might have retarded the course of

the disease. If we were again so fortunate as to make an early diagnosis of primary disease of the pulmonary artery we should search carefully for evidence of a syphilitic basis, the smallest hint of which would be accepted as an encouragement to energetic treatment.

Summary.

Five cases of primary disease of the pulmonary artery are reported. In two the lesion was congenital. In the third and fourth an arteriosclerotic change was found, without obvious cause. In the fifth, the lesion was syphilitic. Arguments in support of the view that there is an inherited factor in the causation of such lesions as were found in the third and fourth cases are brought forward.

The effect of disease of the pulmonary artery on the work of the circulation is discussed.

The clinical picture accompanying progressive degeneration of the pulmonary artery is thought to be definite enough to furnish opportunities of diagnosis.

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DESCRIPTION OF PLATES 2–5.

PLATE 2, FIG. 1. *Lung and Heart from Case I.* Showing widening of pulmonary artery and congenital bronchiectasis.

FIG. 2. *Heart from Case IV.* Showing dilatation and hypertrophy of the right ventricle.

PLATE 3, FIG. 3. *Pulmonary Artery from Case IV.* Primary pulmonary arteriosclerosis. Branch of artery in lung root: *a*, under low magnification, showing subintimal proliferation; *b*, higher power view at point of maximum thickening.

FIG. 4. *Pulmonary Artery from Case V.* Syphilitic disease of pulmonary artery. An artery in the lung root showing considerable subintimal thickening, invasion of the media, and an adventitial gumma (at G).

PLATE 4, FIG. 5. *Primary Arteriosclerosis of the Pulmonary Arteries.*[2] On the left, where sclerosis is relatively slight, the vessel shows a compact longitudinal, subintimal elastic layer (L. E.). On the right, where there is pronounced subintimal thickening, this layer at first sight appears to be absent, but its indistinct outlines, faintly striated by swollen longitudinal elastic fibres, can be traced through the plaque.

FIG. 6. *Primary Arteriosclerosis of the Pulmonary Arteries.*[2] Longitudinal section of a lobar branch 4 mm. in diameter. Stained by orcein. A well-developed subintimal elastic layer is seen which becomes indistinct and swollen as the intima thickens. The degree of intimal swelling in this section is relatively slight.

PLATE 5, FIG. 7. *Pulmonary Artery from Case V.* Syphilitic disease of pulmonary artery. Wall of the same vessel as in Fig. 4, under higher power.

FIG. 8. *Pulmonary Artery from Case V.* *a*, Gummatous arteritis of pulmonary artery, showing fibrosis of interalveolar septa and endarteritis of vessels; *b* and *c*, vessels of interalveolar septa, showing occlusion by endarteritis and thrombosis.

[2] Micro-photographs, mounted diagrammatically, of longitudinal sections of a lobar branch of the pulmonary artery, 4 mm. in diameter, lying in the lung root. Stained by orcein. Magnification, $\times 55$.

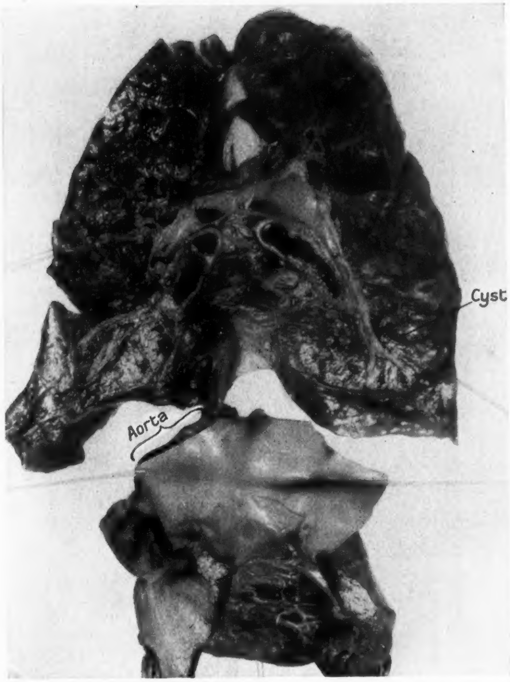


FIG. 1. Lung and heart from Case 1. Aorta and pulmonary artery (both opened). Circumference of latter (in front) about twice that of former (behind).

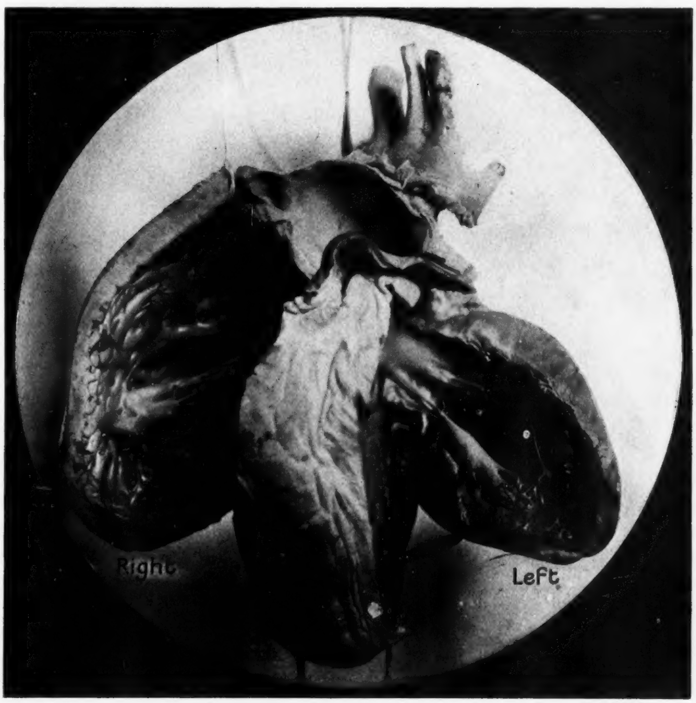
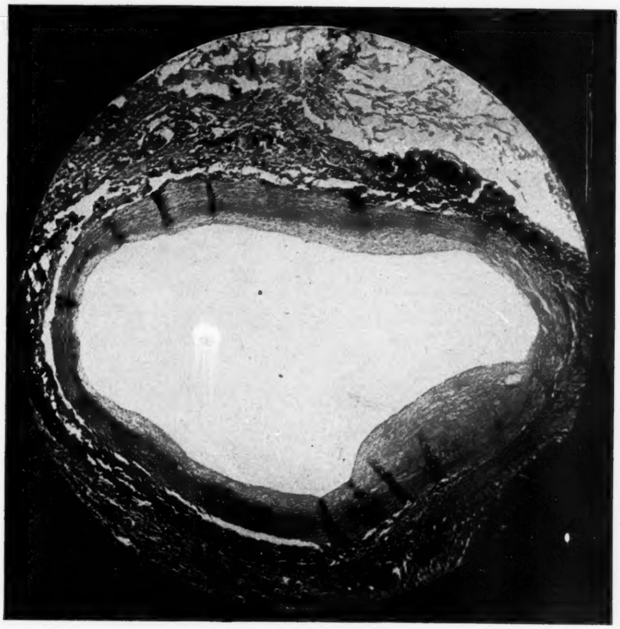


FIG. 2. Heart in primary pulmonary arteriosclerosis, seen from the front.



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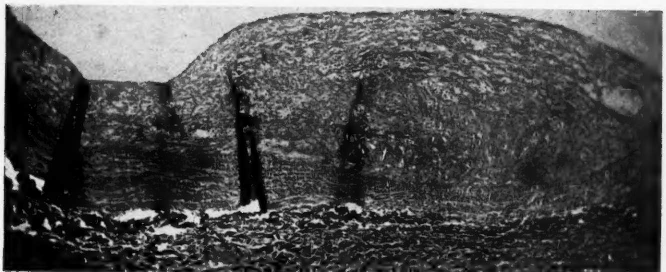

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Case 4.

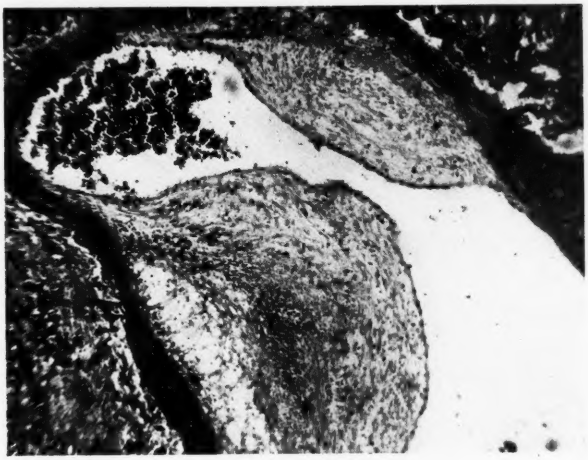
FIG. 3. Primary pulmonary arteriosclerosis.

Case 5.

FIG. 4. Syphilitic disease of pulmonary artery.

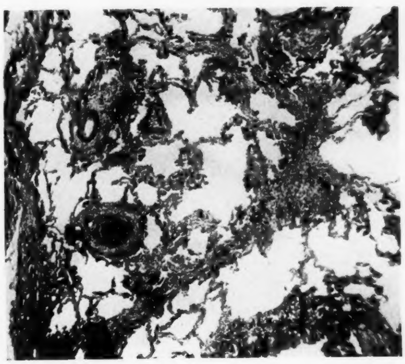
FIG. 5. Primary arteriosclerosis of the pulmonary arteries.

FIG. 6. Primary arteriosclerosis of pulmonary arteries.



Case 5.

FIG. 7. Syphilitic disease of pulmonary artery. Wall of the same vessel as in Fig. 4, under higher power.



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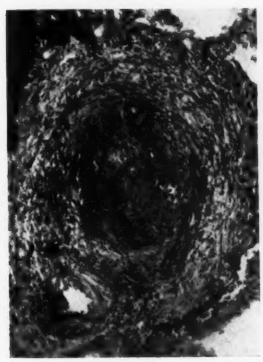

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Case 5.

FIG. 8. Gummatous arteritis of pulmonary artery.

OBSERVATIONS ON THE EXCRETION OF WATER AND CHLORIDE AFTER THEIR ORAL ADMINISTRATION [1]

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THE regulation of the interchange of the fluids of the body in normal and pathological conditions is one of the most fascinating problems in medicine, and a great deal of study has been given to the subject. There are many factors which play a part in this mechanism, but two of the most important are the intake and elimination of water and sodium chloride. It is recognized that these are intimately related to the problem of oedema, and recently full reviews of this subject have been published by Loeb (9) and MacLean (10). The tendency at the moment is to regard other factors, such as the plasma protein, the state of the capillary wall, and the capillary pressure, as being of somewhat greater importance than the intake and output of water and chloride, but there is little doubt that the latter have a profound influence. The beneficial results to be obtained in many cases of oedema by reducing the salt and water intake show this clearly. Evidence has also been brought forward to show that it is the Na ion and not the Cl ion which is the important factor in the action of sodium chloride in oedema. Water and salt are also of considerable importance in nephritis, and attempts have been made to study kidney function by estimating the chloride concentration of the urine after the oral administration of NaCl or KCl. De Wesselow (14) has recently reviewed the literature of this subject and carried out an investigation in cases of nephritis of different types. In azotaemic nephritis he found that impairment of urea and chloride concentration ran parallel. In nephritis with oedema there were two types of response. The chloride concentration in the plasma and in the urine were low in parenchymatous nephritis, and he thought the oedema was of extra-renal origin, while in acute nephritis, in which the chloride concentration was normal or approximated normal, he considered the oedema due to failure of the kidney to excrete water. Leiter (8) has recently brought forward evidence to show that the chloride concentration in the urine after the ingestion of KCl depends largely on the salt content of the diet during the days preceding the test. He found only an

[1] Received May 27, 1927.

[2] Working on behalf of the Medical Research Council.

approximation of the chloride concentration to the urea concentration after the de Wesselow test, but no exact parallelism.

Before a study of water and chloride metabolism can be carried out in pathological conditions, it is necessary to study the changes which take place under normal conditions. A large amount of experimental work has been done in which chloride of various concentrations was injected intravenously and its excretion studied, but this is not of the same importance in its application to the problems in man as the changes which take place following oral administration. Cushny (5) has recently reviewed the literature on the excretion of sodium chloride and water under normal conditions. When a large amount of water is taken by mouth there is a profound diuresis and a diminished concentration of all the urinary constituents. He states that sodium chloride by mouth, even in considerable quantities, often fails to increase the urine volume, but appears in greater concentration. In other cases there is an increase in urine volume without much rise in chloride concentration, while in others diuresis takes place and the concentration of chloride is increased. Ambard and Weill (3) established the threshold value for the excretion of chloride as 5·62 grm. per litre of plasma, and formulated a law for the excretion of chloride. They also considered that the urea excretion formed a basis for the excretion of sodium chloride. MacLean (11) found that the rate of chloride and urea excretion was determined by their concentration in the blood, the weight of water excretion, and indirectly by the weight of the subject. He confirmed the threshold value found by Ambard, although slight variations from it took place. He did not find that the urea excretion gave any basis for calculating the rate of chloride excretion.

The maximal concentrations of chloride in the urine of man which have been reported by different authors varied between 1 and 1·35 grm. per cent. Cl. De Wesselow (14) found that a figure approximating the maximum concentration of chloride in the urine could be obtained by giving 4 grm. KCl in 200 c.c. of water by mouth. In twenty-five out of twenty-eight examinations in normal subjects a concentration above 0·8 grm. per cent. Cl was obtained. Addis and Foster (1) state that there is no limit to the extent to which the kidney can concentrate. They found that the volume of urine varied in almost direct proportion to the sum of the chloride, urea, and phosphate excreted. Adolph (2) says that the sum of urea and chloride excretion tends to be constant for all rates of water excretion. In his investigation no diuresis took place after drinking normal saline. Baird and Haldane (4) found that after the ingestion of salt the greater part of the salt was stored in the tissues with less water than was necessary to reduce it to isotonicity, and that this salt was only slowly given up thereafter. Davies, Haldane, and Kennaway (6) state that chloride and bicarbonate seem to be antagonistic to one another. When given together neither reached the maximum concentration possible, but the sum of both together was equal to the maximum of either alone. The maximum concentration of chloride and bicarbonate was within wide limits independent of the total molecular concentration of the urine.

The present investigation was undertaken to study the effect of the oral administration of water, normal saline, and concentrated sodium chloride on the excretion of water, chloride, and urea by normal individuals.

Method of Investigation.

The observations were made on six subjects who were suffering from slight chronic arthritis and minor nervous disorders. The cardio-vascular, gastro-intestinal, and urinary systems presented no abnormality, so that for the purposes of this investigation they may be considered normal subjects. All the observations were carried out under basal conditions. Patients were at rest in bed and received no food from eight o'clock the previous evening until the observations were completed. During the time they were in hospital each patient received ordinary ward diet, so that their salt intake was previously unrestricted and they all received approximately the same amount. Three types of investigations were carried out on each subject, (1) drinking one litre of water, (2) drinking one litre of normal saline (0·9 per cent. NaCl), (3) 9 grm. NaCl in 40 c.c. of water. The latter was given by duodenal tube in order to avoid vomiting. In some instances the tube did not reach the duodenum—presumably due to no meal having been given—but in these no difficulty arose when the solution was injected slowly over a period of about ten minutes. A urine specimen was collected from 6 to 10 a.m. and then the solution to be studied was given. Thereafter urine specimens were collected hourly for four hours. The urine volume, chloride, and urea concentrations were estimated in each sample. Chloride was estimated by a Volhard titration, and urea by the method of van Slyke and Cullen (13). Chloride was calculated as Cl and urea as urea N.

After 1,000 c.c. of water.

Volume. Before water was given the average urine volume per hour was 35 c.c., the maximum being 55 c.c. and the minimum 18 c.c. After the water was taken a pronounced diuresis set in. This was greatest in the second or third hours (Fig. 1). The average output at the height of the diuresis was 444 c.c., the maximum being 588 c.c. and the minimum 260 c.c. The urine volume in four hours after the test considerably exceeded that before, the average excess being 728 c.c. (Table I). In two subjects the volume in this time slightly exceeded 1,000 c.c., and it is of interest that the volume in these two cases was lower before the test than in the others of the series. However, after deducting the amount normally excreted in four hours it was found in every instance that some of the water which had been taken was retained in the body at the end of the test.

Chloride. Before the test the chloride concentration of the urine varied between 0·657 and 0·920 grm. per cent. Cl, with an average of 0·779 grm. per cent. After the litre of water there was a considerable fall in the chloride concentration.

The lowest concentration was reached in the second or third hours, and it varied between 0·046 and 0·107 grm. per cent., the average being 0·088 grm. per cent. (Fig. 1). Although the urine volume had returned at the end of four hours almost to its original level, the chloride concentration at this time was in every instance considerably below its level before the test. The total amount of chloride excreted in four hours exceeded that in four hours before the test on the average by 0·207 grm. (Table I). In three subjects the excretion was slightly greater than before, and in the other three it was less.

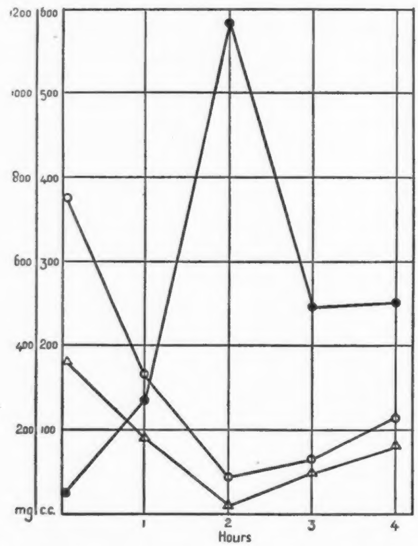

FIG. 1. The urine volume and percentage concentration of chloride and urea after one litre of water.
●——● volume ○——○ chloride △——△ urea.

Urea. The average concentration of urea before the test was 0·495 grm. per cent. urea N, the maximum being 0·680 grm. and the minimum 0·360 grm. During the diuresis there was a marked fall in the urea concentration, which attained its lowest level in the second or third hours (Fig. 1). The lowest concentrations varied between 0·010 and 0·080 grm., the average being 0·060 grm. The concentration of urea at the end of the test was also considerably lower than its original level. There was a fairly close correspondence between the curves obtained for chloride and urea. The total amount of urea excreted during the test was on the average 0·257 grm. greater than was normally passed in a corresponding period (Table I). In only one instance was less urea excreted, and this amount was very small.

After 1,000 c.c. normal saline.

Volume. Before the test the average urine volume was 65 c.c. per hour. The maximum was 110 c.c. and the minimum 21 c.c. Both these figures were

exceptional, in that one was much higher and one much lower than the other four subjects, who were all in the region of the average figure. After saline was given there was in every case an increased urine volume during the first hour, and on two occasions during the second hour also, but in most cases this increase was small. Thereafter the volume rapidly decreased to its previous level, and towards the end of the test was often below it (Fig. 2). During the first hour the output varied between 329 and 61 c.c., the average being 151 c.c. The maximal and minimal figures were obtained in the two cases which had shown the high and low volumes in the control period before the test. The total amount of urine passed in four hours after the test exceeded on the average that

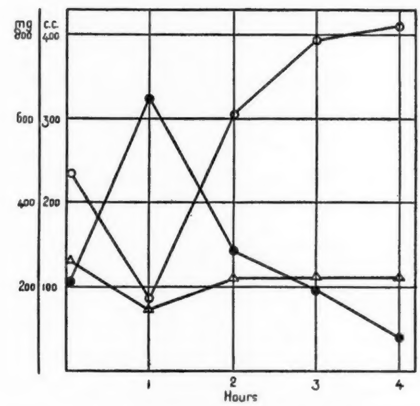

FIG. 2. The urine volume and concentration of chloride and urea after one litre of saline.
●——● volume ○——○ chloride △——△ urea.

in the corresponding period before the test by 95 c.c. (Table II). In one instance the urine volume was less after the test than before, while in another the volume was considerably increased.

Chloride. The chloride concentration before the test varied between 0·347 and 0·884 grm. per cent. Cl, the average being 0·577 grm. per cent. With the increased urine volume during the first hour the chloride concentration fell to some extent, although not to the degree which had taken place during water diuresis. The average of the lowest concentrations obtained was 0·409 gm. per cent., the values ranging between 0·173 and 0·828 grm. per cent. The concentration varied directly with the amount of the diuresis. After the diuresis had passed off it progressively increased until in the third and fourth hours it was above the level before the test (Fig. 2). The average of the highest concentrations obtained was 0·771 grm. per cent., the highest being 0·945 grm. per cent. and the lowest 0·494 grm. per cent. The total quantity of chloride excreted in four hours after saline was given on the average exceeded that in four hours before the test by only 0·358 grm. Cl (Table II). In one instance less chloride was excreted than before the test, while in another the amount was greater than was

usually found. In every case most of the chloride which had been given was retained in the body at the end of four hours. The case which showed the lessened excretion was peculiar in that, although no diuresis was present, the chloride excretion fell in the later stages, in contrast to the others where it attained a higher level than was present during the control period.

Urea. The concentration of urea before the test varied between 0·260 and 0·980 grm. per cent. urea N, the average being 0·497 grm. One case showed a much higher value than the others, and this raised the average to a slight extent. After saline there was as a rule a fall in urea concentration. This might be explained in the early stages by the slight increase in urine volume, but, although its lowest point was as a rule at this time, it never attained its original level even after the diuresis had passed off (Fig. 2). The lowest level to which it fell averaged 0·232 grm. per cent., the minimum being 0·160 grm. per cent. and the maximum 0·360 grm. per cent., while the highest urea concentrations during the test were between 0·220 and 0·740 grm. per cent. with an average of 0·417 grm. per cent. The total quantity of urea excreted after the test was less than before, on the average by 0·158 grm. In one instance it was much less than before, while in another the amount was increased. In two subjects the quantities were practically the same.

After 9 gm. Na Cl.

Volume. Before the test the urine volume per hour varied between 42 and 94 c.c. per hour with an average of 64 c.c. After the salt was taken there was practically no change in the urine volume in four cases, while in two there was some increase during the first hour (Fig. 3). In one of these an increase was also present during the second hour, but thereafter there was a return to about the previous level. The two subjects who showed the increase had the highest urine volumes before the test. The greatest quantity of urine passed in one hour during the test was on the average 92 c.c., the highest being 222 c.c. and the lowest 38 c.c. Except in the two subjects referred to above, the highest level was attained in the second hour. The total amount of urine passed in four hours during the test was on the average 20 c.c. less than in the corresponding period before the test. In only one instance was the quantity greater, while in another it was considerably reduced (Table III).

Chloride. The concentration of chloride before the test was on the average 0·648 grm. per cent. Cl, the minimum value being 0·558 and the maximum 0·788 grm. per cent. After the chloride was given the concentration was never at any time lower than its original level. The highest concentrations obtained varied between 0·680 and 1·082 grm. per cent., with an average of 0·914 grm. per cent. The highest concentrations were obtained in the third and fourth hours (Fig. 3). The total quantity of chloride excreted during the test was in three cases greater than in the corresponding period before the test, while in two others it was less and in the remaining case practically the same. One subject excreted

considerably more and another considerably less than the others. The average amount excreted during the test exceeded that in the corresponding normal period by 0·292 gm. Cl, which shows that most of the salt had been retained (Table III).

Urea. The average urea concentration before the test was 0·605 grm. per cent. urea N, the values varying between 0·370 and 0·940 grm. per cent. In four instances there was a fall in urea concentration throughout the test, in one it rose during the first hour to fall later, and in another it remained practically unchanged

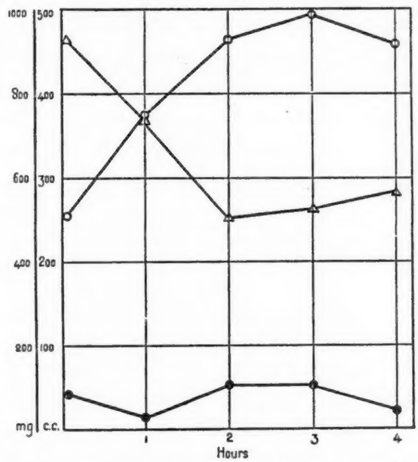

FIG. 3. The urine volume and concentration of chloride and urea after 9 grm. sodium chloride.
●——● volume ○——○ chloride △——△ urea.

throughout (Fig. 3). The highest concentrations were found as a rule at the beginning of the test and lowest at the end. The maximum concentrations during the test varied between 0·320 and 0·980 grm. per cent. with an average of 0·553 grm. per cent., while the lowest concentrations reached were between 0·220 and 0·640 grm. per cent., the average being 0·400 grm. per cent. The total amount of urea excreted in four hours was in every instance less than before the test. The average difference was 0·439 grm. (Table III).

Summary and Discussion.

After a litre of water there was a marked diuresis in every case, but some of the water which had been given was retained at the end of four hours. Assuming that all the water was absorbed, this must have been stored in the tissues, as Haldane and Priestley (7) and Priestley (12) showed that the blood volume, as estimated by their method, was not increased. After a similar amount of normal saline the urine volume was increased to a variable degree during the first hour, although not to the same extent as was seen with water alone. During the remainder of the test, as a rule, no increase in urine volume was present, so that

nearly all the water which had been given as saline was retained. As on the average 905 c.c. of water and 8·409 grm. of chloride calculated as NaCl were retained, the composition of the retained fluid approximated that of normal salt solution, the actual figure being 0·93 per cent. NaCl. When salt alone was given there was no increase in urine volume throughout the test in most cases, but in two a slight diuresis took place during the first hour. In every case except one the urine volume was less in four hours than it had been in the corresponding period before the test. When one compares the water excretion with the salt excretion, it is seen that only a small amount of the salt taken was excreted, while the urine volume was only slightly reduced. Salt must thus have been retained in the body without the retention of the amount of water which would be necessary to reduce it to isotonicity. Probably most of it was stored in the tissues.

The chloride concentration was diminished in correspondence with the diuresis in the case of water administration, but the total output of chloride varied—in three cases it was slightly less and in the others slightly greater than the normal output. After saline the concentration showed a slight fall at first, but in the later stages it was increased, while the total amount excreted was only slightly greater than that normally excreted in four hours. When one studies the concentration it is found that the excretion of water and salt did not follow the same curve. In the early stages water was increased and chloride was reduced, while later chloride was considerably increased compared to water. The changes which took place after saline tended to resemble in the early stages those seen after water alone, while in the later part of the test they approximated those seen after salt alone. The average highest concentration of chloride was about 0·2 gm. per cent. less than was attained after NaCl alone, but in three cases the correspondence was closer. The concentration of chloride after sodium chloride alone was increased throughout the test, and the maximum values obtained corresponded in most cases to those obtained by other authors. In two cases of the series the highest concentrations were 0·680 and 0·713 grm. per cent. These were considerably less than the other cases, when the maximal concentrations were about 1·0 grm. per cent. No reason can be given for the low concentrations in these two subjects. One had shown a low concentration after the saline test, but in the other the response to this test was similar to the others of the series. The total quantity of chloride excreted during the test was on the average only slightly greater, and in two cases was less than before the test, so that nearly all the salt was retained.

In the water test urea concentration fell during the diuresis and the total amount excreted was slightly increased. After saline the concentration was lower throughout the test than before, while the total output showed a slight fall. Following salt alone the concentration was as a rule slightly lessened, while the total amount excreted was diminished in every instance.

Several factors are involved in the mechanism of fluid distribution in the body after the oral administration of a substance which tends to alter the water

balance of the body; (1) its absorption, (2) its concentration in the blood and the corresponding blood volume, (3) its passage from the blood into the body tissues or its excretion in the urine. One thus sees that not only the excretion of the various constituents in the urine but also the corresponding alterations which took place in the blood must be studied before an explanation can be found of the mechanism which was responsible for the various changes observed in the different tests. The purpose of the investigation was, however, to make a comparative study of the tests in normal subjects, in the hope that when they were applied to cases of cardiac and renal disease further light might be thrown on the changes which had taken place in these conditions.

Conclusions.

1. The excretion of water, chloride, and urea after the administration of one litre of water, one litre of saline, and 9 grm. of sodium chloride, respectively, was studied in six patients suffering from slight arthritis and minor nervous disorders, who for the purposes of the investigation may be regarded as normal.

2. The urine volume was increased after water, increased at first after saline and then fell to about its previous level, while it remained about the normal level throughout after sodium chloride. Almost all the water which had been given was excreted in the water test, while most of it was retained in the saline test.

3. The concentration of chloride was lowered during the water test, lowered at first and then increased in the saline test, and raised throughout after sodium chloride had been given.

4. The total amount of chloride excreted during the test, as compared with the corresponding period before, showed no significant change during the water test. Almost all the sodium chloride was retained in the body at the end of four hours when either saline or sodium chloride were given.

5. The urea concentration was considerably lowered during the water test and to a slight extent also in the saline and sodium chloride tests. The total amount excreted in four hours during the test was slightly greater than normal after water administration, and was decreased to some extent after saline and sodium chloride.

I wish to thank Professor D. Murray Lyon and Professor G. Lovell Gulland for permitting me to use the cases on which the observations were made. The expenses of the investigation were defrayed by a grant from the Earl of Moray Research Fund, Edinburgh University.

TABLE I.

The Amount of Urine, Chloride, and Urea excreted in Four Hours before and after 1,000 c.c. of Water.

Patient.	Volume in c.c.			Chloride in grm. Cl.			Urea in grm. urea N.		
	Before.	After.	Diff.	Before.	After.	Diff.	Before.	After.	Diff.
S.	251	795	+544	2·090	1·998	−0·092	1·710	1·657	−0·053
K.	180	830	+650	1·182	1·364	+0·182	1·008	1·027	+0·019
C.	180	716	+536	1·299	1·255	−0·044	0·648	1·026	+0·378
H.	70	1015	+945	0·644	1·576	+0·932	0·280	0·684	+0·404
R.	180	953	+773	1·418	0·970	−0·448	1·080	1·559	+0·479
O.	108	1031	+923	0·819	1·531	+0·712	0·389	0·706	+0·317
Average	—	—	+728	—	—	+0·207	—	—	+0·257

TABLE II.

The Amount of Urine, Chloride, and Urea excreted in Four Hours before and after 1,000 c.c. Normal Saline.

Patient.	Volume in c.c.			Chloride in grm. Cl.			Urea in grm. urea N.		
	Before.	After.	Diff.	Before.	After.	Diff.	Before.	After.	Diff.
S.	263	305	+42	1·138	2·768	+1·630	1·525	1·418	−0·107
K.	84	121	+37	0·603	0·748	+0·145	0·823	0·729	−0·094
C.	180	273	+93	1·391	1·583	+0·192	0·540	0·735	+0·195
H.	340	271	−69	2·100	1·313	−0·787	1·632	0·688	−0·944
R.	284	579	+295	2·510	2·962	+0·452	1·079	1·076	−0·003
O.	440	613	+173	2·045	2·564	+0·519	1·144	1·150	+0·006
Average	—	—	+95	—	—	+0·358	—	—	−0·158

TABLE III.

The Amount of Urine, Chloride, and Urea excreted in Four Hours before and after 9 grm. Na Cl.

Patient.	Volume in c.c.			Chloride in grm. Cl.			Urea in grm. urea N.		
	Before.	After.	Diff.	Before.	After.	Diff.	Before.	After.	Diff.
S.	200	179	−21	1·515	1·679	+0·164	1·760	1·430	−0·330
K.	314	167	−147	2·476	1·552	−0·924	1·633	0·709	−0·924
C.	135	114	−21	0·778	0·775	−0·003	0·675	0·593	−0·082
H.	334	297	−37	2·077	1·982	−0·095	1·236	0·908	−0·328
R.	367	499	+132	2·048	4·318	+2·270	1·542	1·404	−0·138
O.		141	−27	0·981	1·320	+0·339	1·579	0·705	−0·829
Average	—	—	−20	—	—	+0·292	—	—	−0·439

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THE CLINICAL ERIOMETER [1]

By W. F. EMMONS

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With Plate 6

At the beginning of last century Thomas Young showed that the principle of diffraction of light could be used practically in the measurement of the size of small objects. He applied the method to vegetable spores, to blood-cells, and to the fine threads of fabrics, from which latter use he called his instrument an 'eriometer' or wool-measurer.

In 1924 A. Pijper (1) again applied the diffraction principle to the study of the cells of the blood, and extended its use to the pathological condition pernicious anaemia, in order to detect changes in cell diameter accompanying the disease. As he showed, the diffraction effect can be demonstrated very well by simply holding a blood-smear close to the eye at a distance of four or five feet from a small source of light. By applying a physical formula to measurements obtained from a special optical device, which he describes in detail, and which involves a parallel beam of light and a lens of known focal length, it is possible to calculate from each reading the diameter of the cells on a given smear.

A few preliminary words in explanation of the diffraction principle may be appropriate. It has been found that a small aperture, when placed in a beam of light, can cause diffraction of light, i. e. break it up into successive bands of its component colours if the light is polychromatic, or into a series of maxima and minima if the light is monochromatic. The intensity due to rays diffracted through a small angle θ is approximately proportional to [2]

$$\left[\frac{J_1(z)}{z}\right]^2,$$

where

$$z = \frac{\pi d \sin\theta}{\lambda}, \quad . \quad . \quad . \quad . \quad . \quad . \qquad (1)$$

d being the diameter of the aperture and λ the wave-length of light. The condition for maximum intensity is that z shall be a root of $J_2(z) = 0$.

[1] Received July 26, 1927.

[2] Cf. R. W. Wood, *Physical Optics*, chap. vii; *Encyclopedia Britannica*, art. 'Diffraction'.

Thus the Sth bright ring of the diffraction pattern (reckoning from the central bright spot outwards) corresponds to

$$z = \pi K_s, \qquad (2)$$

where K_s is given in the following table:

S	K_s
1	1·635
2	2·679
3	3·699

In the case of n similar apertures distributed at random over a screen, the diffraction pattern remains unaltered, except for an n-fold increase of intensity.

Further, by Babinet's Principle, the pattern remains unchanged at points outside the image of the source when the screen is removed and the apertures replaced by opaque disks of similar form. This allows us to make use of (1) to calculate the diameter of the disks.

If D_s be the diameter of the Sth bright ring formed in the focal plane, and f be the focal length of the lens,

$$\sin\theta = \frac{\frac{D_s}{2}}{\sqrt{\left(\frac{D_s}{2}\right)^2 + f^2}} \qquad (3)$$

Using (2) and (3) in one we obtain

$$d = \frac{K_s \lambda \sqrt{D_s^2 + 4f^2}}{D_s}, \qquad (4)$$

where K_s is found from the above table.

If polychromatic light is used the same reasoning holds, the only difference being that the dark spaces are now occupied by the other colours in their spectral sequence.

An ordinary blood-smear affords the type of screen mentioned in the discussion above, viz. small disks scattered at random in one plane. Fig. 1 represents what takes place when such a screen is interposed in a parallel beam of monochromatic light. A single blood-cell AB of diameter d is represented as causing diffraction of the light through the angle θ. A lens brings the diffracted rays to a focus at the point P on the screen S_1, forming a corona or maximum of diameter D. (Fig. 2, Pl. 6 is a photograph of the actual appearance of the diffraction pattern with monochromatic light.) By measuring D and inserting this value in equation (4) one obtains a value for d, the diameter of the cells themselves. A curve may be drawn with D as abscissae and d for ordinates, which greatly facilitates the use of the instrument described by Pijper and avoids his long and laborious method of calculating each result individually. The curve is found to hold accurately for particles ranging in size from that of the tiny spores of the puff-ball to that of the much larger human red blood-cell. This range embraces the sizes of all the known mammalian erythrocytes.

Were it possible to orient the oval corpuscles of the non-mammalian vertebrates in such a way that their long diameters lay in one fixed direction, one would obtain from such blood an oval corona whose short diameter would correspond to the long diameter of the corpuscle, and vice versa. While a certain degree of orientation does occur in the making of a smear of oval corpuscles (of fowl or frog) with the production of an obscure oval corona, the difficulty of accurately orienting these corpuscles renders the method inapplicable to them. At the same time it is applicable to the whole mammalian phylum with the exception of the Camelidae.

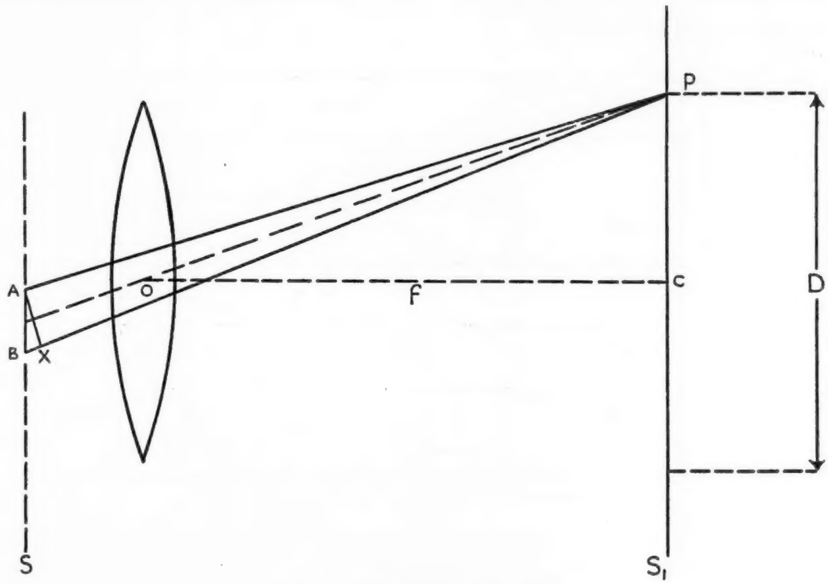

FIG. 1. For description see text.

The eriometer determinations of cell-diameter were checked by measuring the shadows of the cells projected on a screen. The cells were projected along with the rulings of a haemocytometer, care being taken to have the rulings and the cells in one and the same plane. Using a large number of cells and reducing the measurements to their real value, one found a very satisfactory agreement between the eriometer and the screen readings, as the table on p. 86 shows.

An outstanding and valuable feature of the eriometer is of course that its coronae are the composite of tens of thousands of individual cell coronae as against at best the few hundred measurements that can be made directly.

The instrument as designed by Pijper has certain disadvantages. It is bulky. It requires a very intense illumination. The readings obtained involve in each case a troublesome calculation. His apparatus is in short a laboratory rather than a clinical instrument.

An interesting variation of Pijper's instrument has recently been described

by W. G. Millar (2), who, instead of bringing the coronae to a focus on a ground glass screen, observes the diffracted light through a telescope so arranged as to measure the angle through which the light is diffracted. The apparatus is at least as complicated as that of Pijper and involves a similar calculation. Millar provides a valuable discussion of probable sources of error, showing for one thing that the spaces between the cells do not affect the ultimate result. He also proves an interesting point, namely, that the diffraction method reveals no difference of dimension in cells immersed in a citrate plasma as compared with the cells on a dried smear; and he argues from this discrepancy and other evidence that the diffraction method does not give a reliable means of determining the absolute size of erythrocytes.

Animal	Diam. μ		
	E.	M.	B
Cat	5.6	5.7	5.7
Rabbit	6.6	6.5	6.6
Dog	7.18	7.16	7.2
Human	7.9	7.95	7.8

FIG. 3. Table of comparative blood-cell measurements—E, by the eriometer; M, by projection; B, from modern text-books.

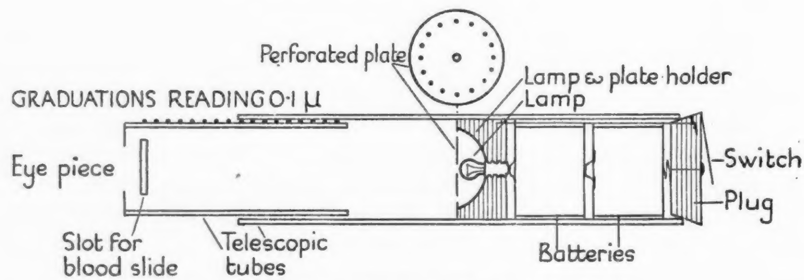

FIG. 4. Diagram of mechanism of the clinical eriometer.

While studying a description of Young's original instrument (see e.g. Preston's *Light*, 2nd ed., p. 222) the idea occurred to the writer of reducing the dimensions of the apparatus and of taking advantage of Young's method of varying the distance of the light, and so of constructing a compact and portable instrument for clinical use. Such is the apparatus here described and designated by Young's name as the eriometer. It consists essentially of two telescopic tubes. The larger, 10 inches in length, is fitted (Fig. 4) with two small dry cells, and

with electric bulb and switch, like an ordinary flashlight. Immediately in front of the electric filament is placed a disk perforated near its periphery by a ring of holes and with one hole at its centre. By this arrangement direct illumination is obtained through the central hole, and an indirect and consequently dimmer light from the holes at the periphery. The other tube, which telescopes completely into the first, carries the blood-slide and is graduated to read directly the diameter of the cells in the smear.

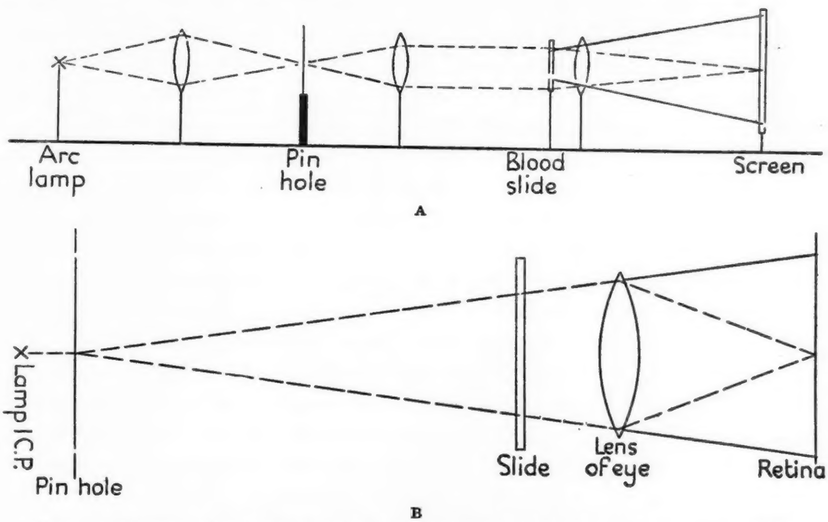

FIG. 5. Diagram showing the optical arrangement in the eriometer. A, non-portable form; B, clinical form.

The principle of the device depends upon the fact that the size of the corona varies with the two factors, viz. the size of the cell and its distance from the light. As Thomas Young showed, the size of the coronae varies inversely as the size of the particles; also inversely as their distance from the source of light. Now if the size of the coronae is kept constant by making it coincide with the peripheral ring of holes, then the size of the particles will be found to vary directly as their distance from the source of light. In other words, if C represents any corona diameter, D the diameter of the cells, and L their distance from the source of light, then

$$C \propto \frac{1}{D}$$

$$\text{and } C \propto \frac{1}{L}$$

$$\therefore\ D \propto L \text{ when } C \text{ is constant.}$$

The non-portable type of apparatus, such as that of Pijper and that of Millar, uses only the first of these relationships, and consequently requires conversion of the inverse proportion by calculation. The present instrument (Pl. 6, Fig. 3) obviates this difficulty by the automatic conversion to a direct proportion due

to the second inverse ratio, and obtain our readings in terms of actual diameters of the particles under examination. Other advantages are its portability, its lightness, and the elimination of all lenses or other intricate optical equipment. The instrument, of course, requires to be calibrated. Calibration is performed with the help of the larger instrument, which gives measurements in absolute units.

It is a very simple matter to operate the instrument. A blood-smear is made in the usual manner and placed in the slot provided for it. The observer, looking into the end of the tube, brings the particular corona for which the instrument is calibrated (red, green, or blue) to coincide with the peripheral ring of holes in the disk by adjusting the telescopic tubes. The diameter of the cells may then be read off from the side of the instrument with an accuracy of $0{\cdot}1\ \mu$.

In making the blood-smear no particular precautions are required so long as a clear sharp corona is obtained. If the blood is smeared too rapidly or from too large a drop, the layer of cells may be so thick that no coronae are seen. The rate of drying of the smear has no influence. With a given smear the size of the coronae remains constant for an indefinite period (at least as long as two years in the experience of the writer).

It is well known that the cells in any given blood sample are not all of the same diameter. This was well shown by Price-Jones (4), and later by Campbell (5) and by Grosh and Stifel (6), all of whom plotted numbers against diameters. In each blood sample was found a certain number of microcytes, and of macrocytes with the great majority of the cells lying between these extremes and forming a pinnacle to the curve, as shown in Fig. 6. The method of Price-Jones was to measure a large number of cells singly and then to plot the curve. He showed that the form of the plotted curve may vary from the normal under certain conditions. For instance, in pernicious anaemia the peak of the curve is shifted towards the region of larger diameters, a fact which tallies well with the familiar increase in corpuscle *volume* known to accompany the same condition. The Price-Jones method, while very accurate and significant for diagnosis, naturally entails much time and labour. It is here that the eriometer may prove of clinical value, for it is the position of this important part of the Price-Jones curve that the instrument registers.

It is obvious that each cell throws its own coronae. If, for the sake of argument, we imagine no two cells to be of equal size, but that they gradually increase from small to large, then no coronae are possible because several different colours fall on any given spot. On the other hand, when coronae are present, the intensity of the light (considered for the moment as monochromatic) at any point is directly proportional to the number of cells of the corresponding size. Therefore the point of maximum intensity indicates the mode or characteristic diameter of all the cells present. The mode diameter is not necessarily the mathematical average, but it is just this mode or characteristic diameter that the peak of the Price-Jones curve itself exhibits. In a later paper on the clinical use of the instrument it will be shown that when applied to a large series of various clinical conditions

it is easily capable of picking out those diagnosed by other means as pernicious anaemia.

A modification of the instrument is being constructed in which the dimensions are further reduced, and the electric light and cells discarded. In this modification a lens is inserted and the instrument is simply directed at an ordinary window or other light source.

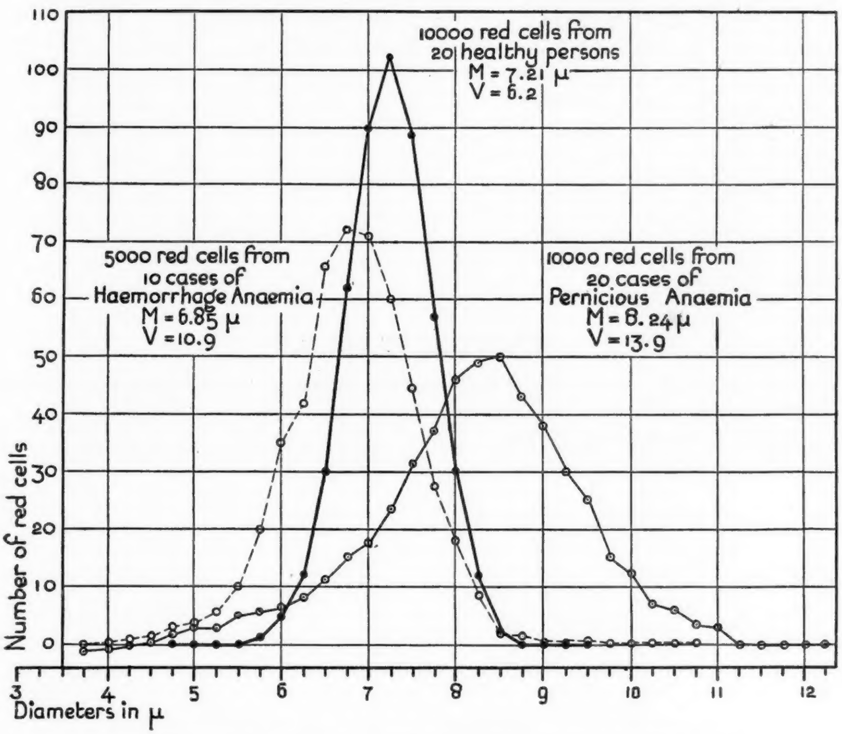

Fig. 6. Curves copied from Price-Jones's paper, showing characteristic blood-cell diameter in various conditions.

Summary.

A small portable instrument is described which will give the characteristic or mode diameter of cells in a dried blood-smear with an accuracy of 0·1 μ. The result is read off directly on the calibrated instrument at the bedside.

I wish to express my gratitude to Professor L. V. King and to Mr. B. Priestman of the Department of Physics of McGill University, and to Professor John Tait of this Department, for aid in this research.

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DESCRIPTION OF PLATE.

PLATE 6, FIG. 2. Photograph of the diffraction pattern, monochromatic light, showing the maxima and minima.

Fig. 3. Photograph of eriometer.

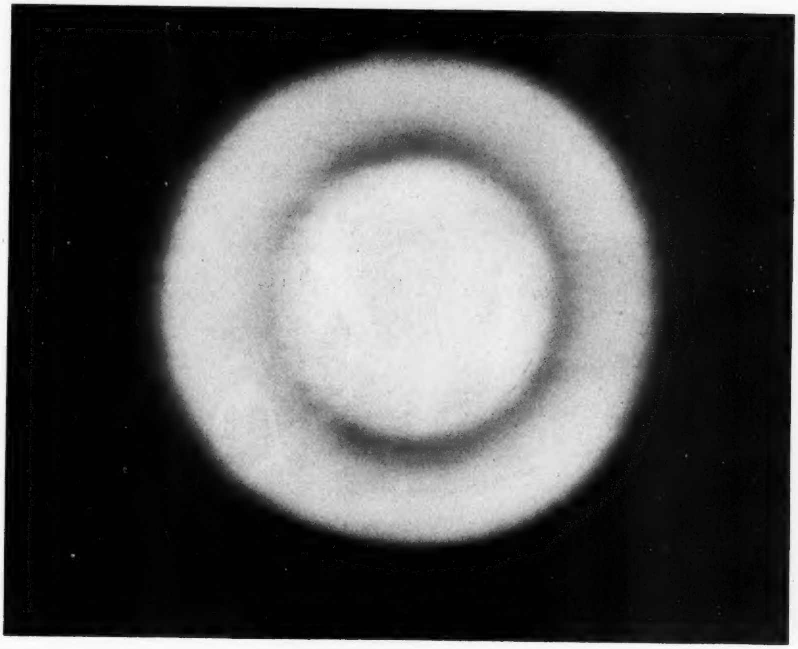

Fig. 2

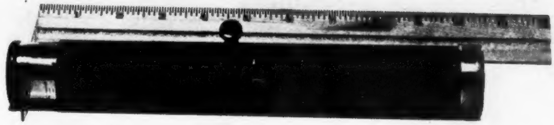

Fig. 3

GLYCOLYSIS IN CEREBRO-SPINAL FLUID AND ITS CLINICAL SIGNIFICANCE[1]

By KATHLEEN CHEVASSUT

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Introduction.

In the early part of 1924 certain observations (unpublished) were made by Dr. J. A. Braxton Hicks (Director of the John Burford Carlill Pathological Laboratories) on the variation in the glucose content of the same specimen of cerebro-spinal fluid examined on different days. At that time it was not possible to develop these preliminary observations. Later in the same year definite research on the subject was carried out by the author under the direction of Dr. Braxton Hicks, and in view of the exceptional facilities for obtaining cerebro-spinal fluid in considerable volume from all varieties of cases, opportunity was taken to subject the question to systematic investigation and to determine, both qualitatively and quantitatively, the carbohydrate content of the cerebro-spinal fluid.

A reference to a large number of previous estimations and to figures recorded in the literature on the subject revealed a remarkable divergence of opinion as to normal values on the part of other workers, leading naturally to much doubt and discussion not only regarding the nature of the reducing substance but also the amount, both in normal and pathological conditions.

From a clinical point of view accurate knowledge on this point is clearly essential before apparent increase or decrease in the sugar content can be of any diagnostic value. Thus, if one considers that according to the present state of knowledge, the normal sugar content is accepted as ranging from 0·037 to 0·148 per cent. (1), the fallacy in attaching any diagnostic significance to a supposed increase in encephalitis lethargica, or decrease in meningitis, for example, is obvious.

It is essential in the investigation of such a subject to draw conclusions from results obtained from normal fluids only, and such has been the aim throughout this work, those obtained from pathological fluids being used only in so far as they throw light on the various factors affecting the sugar content. It is illogical to divide fluids, as Levinson does, into meningitic and non-meningitic, and assume that the latter group of fluids may be taken as normal from the point of view of chemical investigations. Both neoplasms of the brain and encephalitis are examples of the many pathological conditions unassociated with any meningeal

[1] Received July 26, 1927.

involvement, but in which, nevertheless, the cerebro-spinal fluid can be easily shown to be grossly abnormal.

It is equally misleading to assume that a fluid is necessarily normal because it is obtained from a patient apparently free from disease as far as the nervous system is concerned. The excess of urea frequently present in the cerebro-spinal fluid of an individual suffering from uraemia or chronic interstitial nephritis is an example of the error involved in such an assumption. Whether a fluid is normal or not can only be decided by routine examination. The possibility of any alteration in the various constituents of the blood affecting those of the cerebro-spinal fluid must also be taken into account. For example, the figures 0·048–0·058 per cent., frequently quoted as representing the normal sugar content of the cerebro-spinal fluid, are those obtained by Mestrezat (2) in a series of fluids withdrawn prior to stovaine anaesthesia. As Greenfield (3) points out, in such patients prepared for operation the blood-sugar was probably subnormal, and since the amount of sugar in the cerebro-spinal fluid is so intimately dependent on that in the blood, reliance cannot be placed on figures obtained under such conditions.

Experimental Investigations.

It is now generally accepted, as the result of the observations of Nawratski (4) and Denigès (5) in 1897, that the copper-reducing substance is glucose, and in the present research it was found that the latter is the only monosaccharide present in cerebro-spinal fluid.

That the sugar content of normal cerebro-spinal fluid diminishes immediately after withdrawal, and subsequently at varying intervals, can be seen by reference to the following results, which are representative of some 200 estimations, carried out by MacLean's method, on ventricular, cisternal, and lumbar fluids, obtained by triple puncture and kept under sterile conditions at 37° C.

Hours (after withdrawal).	Percentage of Sugar. Ventricular Fluid.	Cisternal Fluid.	Lumbar Fluid.
0	0·175	0·15	0·1
1	0·15	0·143	0·095
2	0·137	0·137	0·086
3	0·12	0·13	0·08
4	0·11	0·125	0·075
5	0·09	0·121	0·07
7	0·086	0·105	0·068
11	0·075	0·1	0·06
16	0·06	0·093	—
22	0·045	0·086	0·05
27	0·036	0·08	—
30	0·03	0·076	0·045
43	—	0·068	—
49	0·02	0·062	0·035
67	0·01	0·05	0·031
74	—	0·043	0·025
88	—	0·037	0·018
96	—	0·025	0·015
120	—	0·018	0·01

The more rapid disappearance of sugar from ventricular fluid as compared with that from the cisternal or lumbar fluid is evident from the table.

Up to the present time no observer has taken into account this diminution in the sugar content after withdrawal, and therefore it is not surprising to find great variations in the figures given as representing the normal sugar content of the cerebro-spinal fluid. In other words, no authorities take into account the important factor of time elapsing between withdrawal and examination for sugar in the interpretation of their results.

Three possible causes of this variation in the carbohydrate content of the cerebro-spinal fluid after withdrawal are:

1. *Alkalinity.* It might be supposed that on account of the instability of glucose in alkaline solution, the mere removal of carbon dioxide on standing might, by rendering the fluid more alkaline, lead to a destruction of sugar. In discussing this same question in the case of blood, Lovatt Evans (6) points out that a pH of 9 is inadequate to cause appreciable change and the pH of the cerebro-spinal fluid never goes above 8·6 on standing. That mere alkalinity of the cerebro-spinal fluid is not the cause of the break-down was demonstrated in a large number of fluids by finding that the glucose broke down equally rapidly in sterile specimens which were not allowed to become more alkaline by loss of carbon dioxide, but were kept under such conditions that a pH of 7–7·3 was maintained.

2. The possibility that the disappearance might be due to condensation, with some di- or polysaccharide formation, was eliminated by a series of experiments which demonstrated that no sugar can be recovered on mild hydrolysis with N/10 oxalic acid or 20 per cent. HCl, if the fluid has been standing longer than eighteen hours, proving that polymerization into some more complex compound is not the cause of the disappearance.

3. A third possibility is that enzyme action is responsible for the disappearance, and that this would appear to be the main factor may be deduced from this research.

Up to the present time it has been assumed that the cerebro-spinal fluid does not contain a glycolytic ferment. This assumption is chiefly based on the evidence adduced by Mott (7), who, in 1910, concluded that no glycolysis occurs in cerebro-spinal fluid after withdrawal. He states that he incubated six sterile specimens for two days without the reducing action being materially altered, and that cerebro-spinal fluid may be kept for weeks without the reducing action disappearing. He made quantitative analysis of the sugar by Fehling's gravimetric method, and his conclusions are based on the investigation of eight cases. It is not recorded whether the fluids were normal or not, but in any case it is not surprising that he found that the fluids still reduced Fehling's solution, after standing for a considerable period, since it has been frequently demonstrated in this research that normal cerebro-spinal fluid reduces Fehling's solution when there is no glucose to be detected either by MacLean's method or by the osazone test. Thus, for example, no sugar could be detected by MacLean's method, and no

osazones could be obtained in thirty-eight normal fluids which had stood at 20° C. for six days under sterile conditions, but twenty-two of these still reduced Fehling's solution. Fehling's solution cannot therefore be used for accurate sugar determinations in the cerebro-spinal fluid. This is partly because uric acid is present in a concentration of 1·3 mg. per 100 c.c., but more especially owing to the fact that the sugar breaks down into substances which themselves reduce Fehling's solution. Presumably aldehydes are formed in this break-down, and, since the possible formation of such substances as di-hydroxyacetone must be taken into account, the inaccuracy in attempting to estimate glucose by this method is obvious, since di-hydroxyacetone not only reduces Fehling's solution but does so in the cold.

It is interesting to note in this connexion that several observers (1) have described the presence of acetone in cerebro-spinal fluid which has been standing for some days at room temperature. In this research, however, experiments devised to detect such intermediate products in the break-down of glucose in the cerebro-spinal fluid were not successful, but that reducing substances are formed on standing can be demonstrated by the fact that the copper-reducing power of the cerebro-spinal fluid may be considerable when no glucosazone crystals can be obtained (and when presumably therefore no glucose is present).

It is clear, therefore, that this evidence based on these cases described by Mott in 1910 cannot be accepted as proving that no glycolytic ferment exists in the cerebro-spinal fluid, since he did not take these factors into consideration. The only other observations recorded on the subject are those of Cavazzani (8), who in 1896 found that glycolysis occurred in two fluids from cases of hydrocephalus.

The following experiments would appear to prove definitely that the disappearance of the glucose in sterile cerebro-spinal fluid is due to a glycolytic ferment. Over 200 fluids from the ventricular, cisternal, and lumbar regions formed the basis for this part of the research.

(a) *The effect of temperature.* In an experiment typical of the series performed, 20 c.c. of normal cerebro-spinal fluid were divided into equal volumes, kept in sterile tubes at 0°, 5°, 10°, 18°, 24°, 37°, 40°, 45°, 50°, 55°, 60°; and the amount of sugar present in each sample was estimated at varying intervals of time. The results obtained are shown in Charts I, II, and III. In the case of Chart II, the results from which the graphs are plotted were obtained by estimating the sugar at varying intervals of time, as described above, in a sample to which magnesium carbonate had been added to remove the products of glycolysis.

It will be seen that the rate at which glycolysis occurs is proportional to the temperature. Thus it proceeds most rapidly at 37°, which is therefore the optimum temperature. At room temperature it takes five to eight days to disappear, while at temperatures of 0° C. and 100° C. glycolysis is inhibited. At 60° also the glycolysis is inhibited, but there is a slight drop in the first few hours from 0·15 to 0·125 in the percentage of sugar. Presumably this is due to the action of the enzyme before destruction. As has been pointed out by

Bayliss (9), however quickly the temperature is raised, the enzyme is not at once destroyed, but acts with great energy owing to the rise of temperature.

(b) *Specificity of the enzyme causing glycolysis.* In Chart IV is seen the effect of adding glucose so that it is present in a concentration of 0·1 per cent. when all the glucose originally present in the cerebro-spinal fluid has disappeared. It will be noticed that it disappears more rapidly than the glucose normally

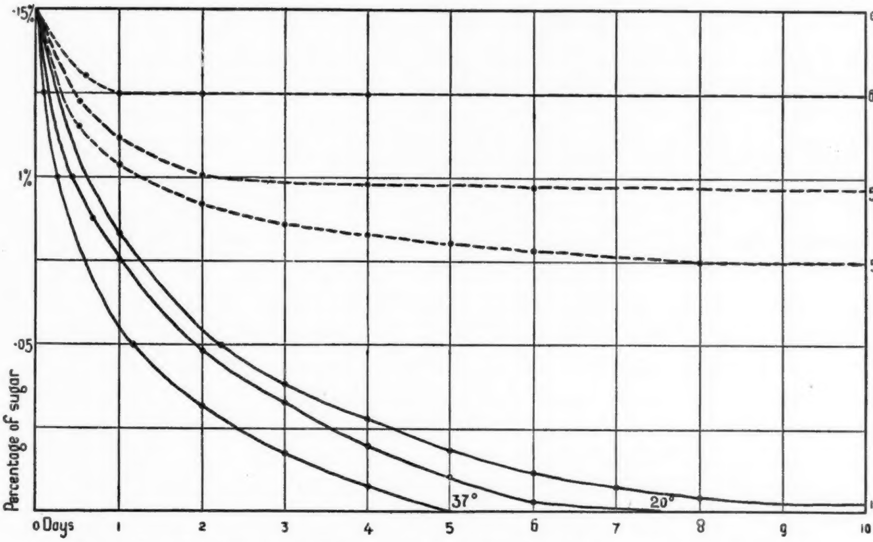

CHART I. Showing effect of temperature on glycolysis in normal cerebro-spinal fluid.

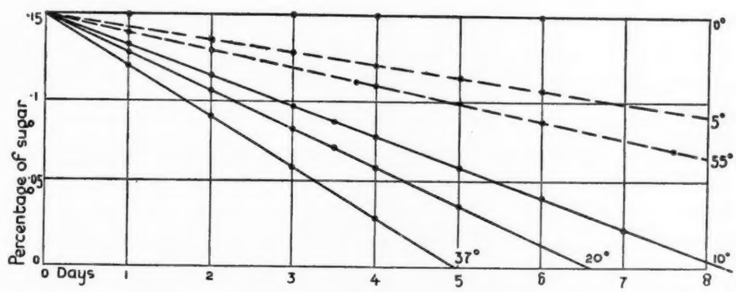

CHART II. Showing the effect of temperature on glycolysis in normal cerebro-spinal fluid to which had been added magnesium carbonate.

present in the cerebro-spinal fluid. The effect of different dilutions of the cerebro-spinal fluid, i. e. of the enzyme present, on added glucose is seen in Chart V. From this it is evident that the rate of glycolysis is proportional to the amount of enzyme present. The results of further experiments to demonstrate the specificity of this glycolytic enzyme are represented diagrammatically in Charts IV and V, from which it will be seen that added maltose and lactose can be recovered quantitatively from the cerebro-spinal fluid. These facts appeared to demonstrate

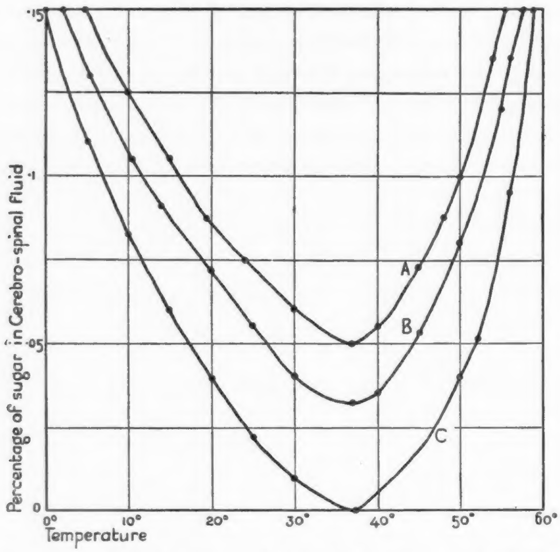

CHART III. A, after 72 hours. B, after 96 hours. C, after 120 hours.

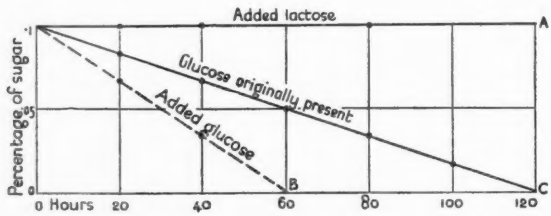

CHART IV. Showing rapid disappearance of glucose added to normal C. S. F.
A represents 1 per cent. lactose added when sugar originally present has disappeared.
B " " glucose " " " " " " "
C " rate of disappearance of original glucose.
Sample of C. S. F. kept at 37° C.
Products of glycolysis removed by magnesium carbonate, hence graphs are in form of straight lines.

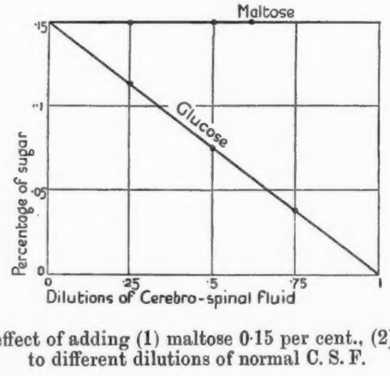

CHART V. Showing effect of adding (1) maltose 0·15 per cent., (2) glucose 0·15 per cent. to different dilutions of normal C. S. F.

that glycolysis, due to a specific glycolytic ferment, is the explanation of the disappearance of sugar in sterile cerebro-spinal fluid after withdrawal.

Glycolysis in pathological fluid is very variable and is not comparable to that occurring in normal fluid. Frequently excess of cells seems to have the effect of accelerating the rate of disappearance of sugar.

In discussing the question of glycolysis in the blood Macleod (10) suggests that glycolysis is an intracorpuscular process, and draws attention to the observation of Levene (11) that suspensions of leucocytes possess strong glycolytic power.

Whether this is the mode of action of the cells or not, it is clear that glycolysis in normal cerebro-spinal fluid is not an intracorpuscular process since it proceeds at a steady rate in the absence of cells. The acceleration of glycolysis by excess of cells probably accounts for the diminished sugar content recorded by some observers in certain cases of dementia paralytica (12).

The experiments described on p. 92 demonstrate that the sugar gradually disappears in normal fluid kept under sterile conditions, while the effect of temperature, disappearance of added glucose, and the form of the curves in Charts I, II, and III, all lead to the conclusion that glycolysis, due to an enzyme specific for glucose and apparently of the nature of zymase, is the most important factor to be taken into account in the investigation of the problem of the carbohydrate content of the cerebro-spinal fluid. It seems probable that herein lies the chief explanation of the divergences of opinion expressed by different observers as regards the sugar content of the cerebro-spinal fluid, their results obviously depending on the time elapsing between withdrawal and examination of the fluid and the conditions under which it is kept during this interval of time.

Lactic Acid Production in Cerebro-spinal Fluid.

The presence of lactic acid in normal cerebro-spinal fluid can be demonstrated 12–24 hours after withdrawal by Hopkins's thiophene reagent or by Uffelmann's reagent. The importance of investigating the relationship between glycolysis and this lactic acid and of estimating the latter was clear at the outset of this work, but the difficulty of finding a suitable method at once presented itself. As A. V. Hill (13) points out, the number and variety of methods which have been tried show that the estimation of lactic acid presents a number of difficulties when present in small quantities.

Of the various methods suggested that of Clausen (14) at first appeared to be the best available, but it possesses the faults of the oxidative methods in general and proved to be far from ideal for the determination of lactic acid in the cerebro-spinal fluid. The following method was therefore devised by Dr. F. M. D. Hocking (Bio-chemist to the John Burford Carlill Research Laboratories), and proved to be specially suitable for this work because the process of glycolysis is arrested at the lactic acid stage.

The method depends on the fact that if lactic acid is added to a suspension of zinc oxide, zinc lactate is formed, and a decrease in the opacity of the suspen-

sion of zinc oxide occurs, proportional to the amount of zinc lactate, and therefore of lactic acid, present. This alteration in opacity is then determined nephelometrically by comparison with a standard solution of zinc oxide. All the estimations of lactic acid were made according to this method, the procedure being as follows: To 5 c.c. of cerebro-spinal fluid is added, immediately after withdrawal, 5 c.c. of a 1 per cent. suspension of zinc oxide. The mixture is kept at 37° C. and the amount of lactic acid produced is measured at definite intervals of time. Thorough shaking of the solutions immediately before comparison is of course essential.

The results obtained by the zinc-lactate nephelometric method show that normal cerebro-spinal fluid contains no lactic acid on withdrawal, and that no appreciable amount is present until 8–12 hours have elapsed. For example, in a typical normal cerebro-spinal fluid containing 0·1 per cent. of sugar and kept at 37° C. the following figures were obtained:

Time in Hours.	*Percentage of Lactic Acid.*
12	Nil
24	0·015
36	0·0274
48	0·049
72	0·084
96	0·104
108	0·104

If the sugar is estimated at the same time as the lactic acid is measured the relation between the two can be accurately determined. From Chart VI, which represents the results thus obtained, it will be seen that the amount of lactic acid finally produced corresponds almost precisely with the original amount of sugar.

These experiments afford additional proof of the activity of a glycolytic ferment in cerebro-spinal fluid after withdrawal.

The presence of lactic acid in cerebro-spinal fluid has been mentioned by several observers, but no theories as to its origin in normal fluid have up to the present been advanced.

Thus in discussing the question of the abnormally low pH of the cerebro-spinal fluid in meningococcal meningitis, Levinson (1) states that he believes it to be due to lactic acid production, but gives no evidence in support of this explanation. In a recent paper on the subject Killian (15) states that five specimens of normal fluid which he examined showed a lactic content of 8–15 mg. per 100 c.c., while in cases of meningococcal meningitis he finds as much as 23–77 mg. per 100 c.c. In the latter case, he compares the amounts of sugar and lactic acid present, and finds that the amount of lactic acid produced does not account for all the sugar lost. This may be due partly to the fact that he uses Clausen's method, which only represents approximately 85 per cent. of the lactic acid actually present: but chiefly because the prevention of the break-down of lactic acid into carbon dioxide, &c., is not provided for, and unless this is done the

amount of lactic acid, when estimated, will appear to be less than it actually is. It is surprising that, although in these cases of meningitis he estimates the sugar and finds it to be decreased, yet he never considers the possibility that lactic acid production in normal cerebro-spinal fluid is actually due to the glycolysis occurring, and he comes to no conclusion in this paper as to why lactic acid should be present in normal cerebro-spinal fluid. As he ignores this possibility he records neither the amount of sugar present in the five normal fluids nor the time elapsing between withdrawal and examination of the fluid.

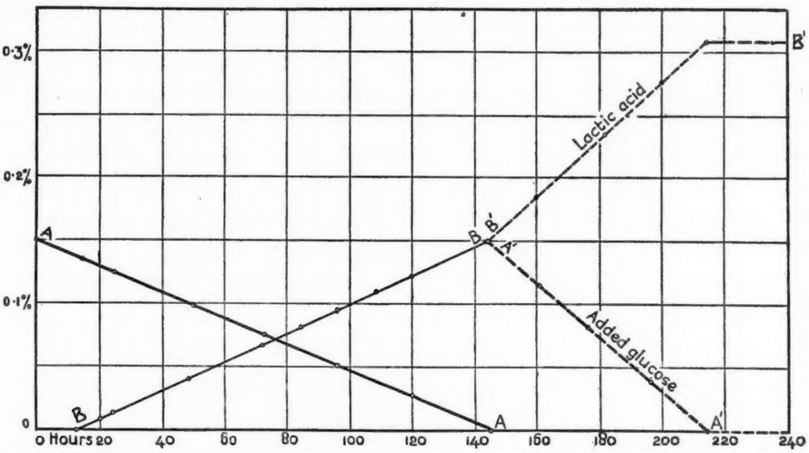

CHART VI. Showing rapid production of lactic acid from glucose added in 0·15 per cent. concentration to normal cerebro-spinal fluid.

A represents rate of disappearance of sugar originally present.
A′ " " " " " added glucose.
B " " " production of lactic acid from original sugar.
B′ " " " " " " " added glucose.
Products of glycolysis removed in each case by presence of zinc oxide.

Chart VI shows the effect of adding an amount of glucose so that it is present in a concentration of 0·15 per cent. after all the sugar originally present in the cerebro-spinal fluid has disappeared, i. e. after 144 hours. It was found that the lactic acid production was much more rapid than in the case of ordinary fluid. Thus reference to Chart VI shows that the lactic acid reaches a maximum of 0·309 per cent. in 72 hours, which means that 0·159 per cent. of lactic acid has been produced in 72 hours, since 0·15 per cent. was present in the fluid originally from the break-down of its own glucose. This result is interesting when correlated with the previous observation (on p. 95), that added glucose disappeared more quickly than that originally present. It seems possible from these results that the glucose in the cerebro-spinal fluid is present not simply as such, but as some more complex compound which must first be broken down before actual glycolysis starts, whereas added glucose simply breaks down straight away, so that lactic acid is more rapidly produced.

A series of observations made on the phosphate content of the cerebro-spinal

fluid are of interest in this connexion. The average amount of inorganic phosphate in normal cerebro-spinal fluid was found, if estimated immediately on withdrawal, to be 1–1·5 mg. per 100 c.c., but in a large series of fluids in which the sugar content was estimated concurrently with inorganic phosphate at varying intervals during glycolysis the percentage of phosphate was invariably found to rise as the sugar content fell, being 3–4 mg. per 100 c.c. after 96–120 hours. A consideration of these observations on the relation between the amounts of sugar, lactic acid, and inorganic phosphate would appear to give some confirmation to the possibility that the sugar in the cerebro-spinal fluid is present as a hexose-phosphoric acid compound and not as free glucose.

Such a theory would necessitate the supposition that two enzymes are involved, (1) hexose-phosphatase and (2) a glycolytic enzyme. In view of the present controversy on the same question as regards the sugar in the blood and elsewhere in the body no opinion is ventured on the matter in the case of the cerebro-spinal fluid. It is interesting, however, to note in this connexion that in just those two conditions in which the glucose of the cerebro-spinal fluid is diminished, namely cases of meningitis and spinal compression (below the lesion), several observers have recorded increase in the percentage of inorganic phosphate in the cerebro-spinal fluid (16).

The Reaction of the Cerebro-spinal Fluid and the Relationship between Glycolysis and Hydrogen-Ion Concentration.

It might be expected that, in consequence of the production of lactic and carbon dioxide by glycolysis, the reaction of the cerebro-spinal fluid would become more acid on standing, but determination of the pH by the Capillator method (17) proved that this is not so. Using this method, investigations were carried out on a series of normal ventricular, cisternal, and lumbar fluids. It was found that the pH of normal cerebro-spinal fluid on withdrawal is 7·3–7·4, i. e. identical with that of the blood. In every sample examined it was found that during the first two hours after withdrawal the pH rapidly increased from 7·3 to 7·9 or 8. In the next twelve hours the change is more gradual, and after twelve hours the pH remains practically constant, the final value, twenty-four hours after withdrawal, being about 8·1–8·5. That this change in reaction was not due either to the effect of the glass of the tube containing the cerebro-spinal fluid, or to formation of ammonia or other alkaline substance in the fluid itself, was proved by comparing the pH of fluid kept in an ordinary sterile tube with a cotton-wool plug, with the pH of the same fluid collected beneath a layer of paraffin and kept tightly corked. After 2–8 hours it was found that the pH of the latter fluid had retained its original value, or had even fallen, while the pH of the fluid in the tube with the cotton-wool plug only had become more alkaline, the pH changing from 7·3 to 8·1.

The hydrogen-ion concentration of the cerebro-spinal fluid has been investigated by many observers. Weston (18) in 1916 found it to vary from 7·9 to 8·3.

Harwitz also in 1916 recorded 8·15–8·3 as the pH. These figures, however, are not reliable, for none of these observers took into account the carbon-dioxide variations occurring, and they failed to recognize the fact that just as loss of carbon dioxide affects the reaction of the blood, so, unless the cerebro-spinal fluid is collected and examined without loss of carbon dioxide, the reaction will appear more alkaline than it really is in the body. Levinson (19) in 1917 was apparently the first observer who took into account the effect of carbon-dioxide variations on the pH of the cerebro-spinal fluid. He drew attention to the fact demonstrated in the above experiments that the change in reaction to the alkaline side of neutrality, which occurs in the fluid on standing, is due to loss of carbon dioxide from the fluid.

The acid-base equilibrium of the cerebro-spinal fluid is discussed by Parsons (20) in a paper published in 1920. These observers also recognizing this effect of loss of CO_2 on the pH collected the fluid so as not to come into contact with the air, and then measured the carbon-dioxide content and the pH at various carbon-dioxide tensions, and found a close correspondence between the carbon-dioxide-combining power and reaction of the fluid. They then proceeded to calculate the pH by Hasselbalch's formula (21). Using the graph constructed by Hasselbalch, because they find very little difference between the pH values thus calculated and those observed experimentally, they conclude (1) that the cerebro-spinal fluid behaves similarly to a sodium bicarbonate solution in this respect, (2) that Hasselbalch's formula can be applied to cerebro-spinal fluid, and (3) that the whole of its combined carbon dioxide is in the form of sodium bicarbonate. This conclusion involves of course the assumption that the hydrogen-ion concentration depends only on the carbon dioxide and the bicarbonate (since the formula depends on this assumption) and leaves out of account the possibility of the existence of other buffers (phosphates, &c.) in the cerebro-spinal fluid. All the fluids they used were pathological, and one-third of them were cases of meningitis, which naturally would show a diminished carbon-dioxide-combining power, as it has been shown that meningitic fluid presents anomalous results in this respect, the acid-base equilibrium being upset (1). They compare the reaction of the cerebro-spinal fluid with 0·02 and 0·03 N solutions of sodium bicarbonate, and although they find the reaction changes more gradually in the cerebro-spinal fluid, they come to the conclusion that it is only slightly more efficiently buffered than a bicarbonate solution. On the contrary, when one considers that glycolysis is occurring, the possibility of which is of course left out of account in their paper, and finds that lactic acid is being produced after the first twelve hours in steadily increasing quantities, it is evident that the cerebro-spinal fluid must be extremely well buffered to maintain a constant pH of about 8. In other words, they do not take into consideration that changes are occurring in the fluid itself, and that when they measure any one pH the value represents not only the effect of the carbon-dioxide tension to which the fluid is exposed, but the combined effect of this and acid production in the cerebro-spinal fluid itself, while the bicarbonate solutions used for comparison

merely represent the effect of the various carbon-dioxide tensions, and the fall in carbon-dioxide capacity which Parsons ascribes to deficient buffering is, in reality, due to production of lactic acid from glucose.

During the first twelve hours after withdrawal the amount of lactic acid produced is not sufficient to cause any change in the pH, and so the only factor concerned is that due to loss of carbon dioxide from the fluid, in consequence of which it becomes more alkaline. Subsequently the effect of production of lactic acid is to depress the proportion of fixed, and raise that of free carbon dioxide, and evidently the escape of carbon dioxide assists in the maintenance of neutrality, for if kept tightly corked the pH of the fluid falls to about 7. This is, of course, quite different from the changes already referred to as occurring in the first few hours after withdrawal, and only refers to changes in the pH occurring after the effect of loss of carbon dioxide has passed off. In the case of meningitis, there is either absence or diminution of the sugar in the cerebro-spinal fluid, and it is found that the pH of such fluid corresponds, on withdrawal, to that which would be found in a sample of normal fluid which had been collected under paraffin and kept tightly corked until it contains an amount of sugar identical with that in the meningitic fluid, the low pH in such conditions depending on the amount of lactic acid present. The mechanism of break-down of sugar in the case of meningitis is, of course, not analogous to that occurring in the normal cerebro-spinal fluid, since it is due to the invading organism, but the relationship between lactic acid produced and sugar remaining is the same. In both cases it is evident that in spite of the acid production, the pH of the cerebro-spinal fluid, owing to the efficiency of its buffer system, does not fall below 7. Thus in many cases of meningitic fluids in which there is no sugar present, the pH on withdrawal is 7–7·1, which is the same value as that attained if normal fluid has been corked thus and left long enough for all the sugar to disappear.

The Carbohydrate Content of the Cerebro-spinal Fluid and its Relation to the Blood-Sugar.

A comparison of the percentages of sugar in fluid from the ventricular, cisternal, and lumbar regions shows that they are not identical, but that the percentage of sugar is invariably higher in normal fluid from the ventricular than that from the cisternal and lumbar regions of the same individual.

All the sugar estimations in this work were carried out by MacLean's method and the samples were examined immediately after withdrawal.

It was found in 140 fluids examined (comprising 22 ventricular, 38 cisternal, and 80 lumbar fluids) that ventricular fluid contains 0·1–0·15 per cent. sugar, while normal, cisternal, and lumbar fluids contain approximately equal amounts of sugar ranging from 0·086–0·095 per cent.

The next step was to compare the concentration of sugar in the cerebro-spinal fluid with that of the blood-sugar, and to establish whether there exists

any definite relationship between the percentage of sugar in the blood and that of the cerebro-spinal fluid from the ventricular, cisternal, and lumbar regions.

The routine method in every case on which ventricular puncture was done was to estimate the blood-sugar immediately before, during, and 5–10 minutes after ventricular puncture had been performed.

It was found in every case that the sugar in the ventricular fluid was equal to that of the blood-sugar before and during the operation. The following are a few of the results obtained:

Percentage of Sugar.

	In Blood.				
	Before Puncture.	10 Mins. later.	In Ventricular Fluid.	Cisternal Fluid.	Lumbar Fluid.
* (1)	0·2	0·29	0·196	0·112	0·1
* (2)	0·195	0·25	0·175	0·15	0·1
* (3)	0·175	0·2	0·175	0·1	0·093
* (4)	0·148	0·24	0·15	0·1	0·093
(5)	0·1	0·162	0·137	0·093	0·093
(6)	0·125	0·193	0·121	0·093	0·086
(7)	0·106	0·175	0·1	0·086	0·086
(8)	0·112	0·175	0·106	0·086	0·086
(9)	0·143	0·2	0·137	0·1	0·093

* These patients had an anaesthetic.

These figures show that if the exact relationship between the amount of sugar in the cerebro-spinal fluid and that in the blood is to be established, it is the ventricular fluid which must be used for comparison, and that when this is done it is found that they are identical within the limits of experimental error.

The relationship between the sugar content of the cerebro-spinal fluid and that of the blood has been investigated by several observers.

Polonovski (22) in 1923 found that although the sugar in lumbar fluid rose and fell with the blood-sugar it never reached the value of the blood-sugar. Thus they found that a fasting level of 0·045–0·086 per cent. was increased by ingestion and absorption of food to 0·105 per cent. and that hyperglycaemia induced by administration of adrenalin was accompanied by a rise of cerebro-spinal fluid sugar, similar in type but slower and to a lesser degree.

Triple puncture, however, reveals the fact that the amount of sugar in the cerebro-spinal fluid is directly dependent on that in the blood, and not only rises and falls with it, but in normal ventricular fluid is invariably equal to it.

Comparison of the percentage of sugar in the ventricular and lumbar fluids in the above table will make it clear why those observers working with lumbar fluid have found the sugar in the latter to rise and fall with that of the blood, but never to equal it.

In cases 1–4 in the table a general anaesthetic was administered, hence the high blood-sugar values and glycosuria occurred in these patients 2–4 hours later. The remainder of the cases had no general anaesthetic. These experiments demonstrated incidentally the interesting fact that ventricular puncture causes hyperglycaemia. That this was not due to emotion is shown by results obtained in patients accustomed to the operation, and by control experiments

on the blood-sugar immediately before and during the operation. It is only the third sample of blood taken 5–10 minutes afterwards which shows excess of sugar. It must be understood in interpreting these results that the whole procedure of ventricular puncture and withdrawal of the fluid only occupies about five minutes. These results suggest that the hyperglycaemia recorded by Claude Bernard as a result of puncture of the floor of the fourth ventricle can be produced by stimulation of any part of the brain, and is not an effect peculiar to puncture of the fourth ventricle only.

From a clinical point of view these comparative observations are of importance in that they throw light on the cause of the increased amount of sugar in the cerebro-spinal fluid in encephalitis lethargica, showing that this is probably always the reflection of a high blood-sugar. Attention was first drawn to a high sugar content in the cerebro-spinal fluid in encephalitis by Netter (23). Since then, owing to the divergent results obtained by different observers, there has been much discussion as to whether or not it is actually raised. If it is realized that the sugar in the cerebro-spinal fluid is inherently dependent on that in the blood there is little difficulty in understanding the reason for the divergences of opinion in this matter. Apparently in encephalitis lethargica there is, as a rule, hyperglycaemia (24); an equivalent rise of sugar occurs in the ventricular fluid, and this is reflected in the sugar content of the lumbar fluid, which increases correspondingly, but always has a lower value than that of the ventricular fluid. That apparently anomalous results in this respect will be misinterpreted unless the blood-sugar is simultaneously estimated is illustrated by the following case of acute encephalitis lethargica. The day after admission to hospital a general anaesthetic was given, triple puncture performed, and the following results obtained:

Blood-sugar before Puncture.	Sugar in Ventricular Fluid.	Sugar in Cisternal Fluid.	Sugar in Lumbar Fluid.
0·2 %	0·195 %	0·1 %	0·1 %

The high blood-sugar was presumably due to the general anaesthetic administered. A week later the same procedure, only without a general anaesthetic, showed these figures:

Blood-sugar.	Sugar in Ventricular Fluid.	Sugar in Cisternal Fluid.	Sugar in Lumbar Fluid.
0·175 %	0·175 %	0·15 %	0·1 %

On the third occasion, however, the patient had had no food for twenty-four hours, and showed a comparatively low blood-sugar and acetone and diacetic acid were present in the urine; the following were the results obtained:

Blood-sugar.	Ventricular Fluid Sugar.	Lumbar Fluid Sugar.
0·093 %	0·09 %	0·075 %
0·086 %	0·09 %	0·062 %

If it were not for the fact that simultaneous examination of the blood revealed a relatively low blood-sugar it might be concluded that the diminished amount of glucose found in the lumbar fluid was in opposition to the theory that the sugar in the cerebro-spinal fluid in encephalitis is increased. But this depends entirely on the blood-sugar, and usually in encephalitis lethargica there is hyperglycaemia, which is reflected in the rise in the sugar content of the cerebro-spinal fluid. Two post-encephalitic cases exhibiting the Parkinsonian syndrome also showed hyperglycaemia, their blood-sugar $2\frac{1}{2}$ hours after a meal showing respectively the following values, 0·175 and 0·186 per cent. In meningitis also there is usually hyperglycaemia (3), but in this case the relationship of the sugar content of the cerebro-spinal fluid to that of the blood cannot be compared, since the sugar in the former is being actually broken down by the invading organism.

Conclusions and Summary.

Normal cerebro-spinal fluid contains a glycolytic ferment which, after withdrawal, gradually causes the glucose present to disappear completely.

This ferment is specific for glucose.

Lactic acid is formed quantitatively during glycolysis, of which it is a product.

Therefore any examination of the cerebro-spinal fluid from the point of view of normality of sugar content can only be of value if made immediately after withdrawal.

The concentration of sugar is 0·1–0·15 per cent. in ventricular, and 0·086–0·93 per cent. in cisternal and lumbar cerebro-spinal fluid.

The concentration of sugar in the cerebro-spinal fluid depends on the blood-sugar level and in ventricular fluid is identical therewith.

The apparent increase in the sugar content of the cerebro-spinal fluid in encephalitis lethargica is merely a reflection of, and dependent upon, the hyperglycaemia usually present in this condition.

All the triple punctures referred to in this work were performed by Sir James Purves-Stewart.

My thanks are due to Dr. Braxton Hicks for his most valuable assistance in this work.

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THE COMPOSITION OF HUMAN BILE AND ITS BEARING UPON STEROL METABOLISM[1]

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Introduction.

WITH the possible exception of milk, bile may be said to be the only normal human secretion known to contain any considerable amount of cholesterol. The cholesterol content has accordingly received a good deal of attention, both out of curiosity as to the purpose it may serve and because of the serious consequences which result when it becomes deposited in the form of gallstones. The object of much of the experimental work has been to learn whether any relationship exists between the sterol content of the bile and that of the blood or the diet.

More recently, interest in the whole subject has been further stimulated by the researches of Wieland (1) and his co-workers. Together with Windaus (2), these investigators have shown that cholesterol and the bile acids are quite close chemical relations. In fact Windaus has virtually *prepared* cholic acid, $C_{24}H_{40}O_5$, from cholesterol, $C_{27}H_{46}O$. This work has led to considerable speculation as to the origin of the bile acids and the synthetic activities that may be involved in their production in the body.

As a first step in dealing with such questions as the above, it seemed to us that it is of considerable importance to have as clear an idea as possible of the amount of these substances present in normal bile and of the variations which may be regarded as physiological. We have accordingly collected together what appear to be the most accurate analyses, and these, supplemented by some data of our own, are used as the basis for the discussion which follows.

For obvious reasons, normal human bile is a somewhat difficult substance to study. Most of the work done so far consists either of analyses from gall-bladder specimens taken *post mortem*, or of the secretion obtained from cases where a fistula has been established. Naturally the material from the first source is often of a more or less pathological nature, while fistula bile can scarcely be regarded as a normal secretion, especially in view of what we know of the 'bile circulation'.

[1] Received November 23, 1926.

[2] Working under the tenure of a Beit Fellowship.

Recently, a third method has been introduced, in which, by means of an Einhorn stomach-tube, samples of bile can be removed from the living subject. Such samples would prove of considerable use in the study of bile, but for quantitative purposes the method seems open to sources of error which must be difficult to obviate. Some results obtained in this way are considered later.

I. *Amount of Bile secreted in Twenty-four Hours.*

The amount of bile which reaches the intestine in a day is a point of considerable interest in the study of sterol metabolism. It cannot be estimated directly, but we have tried to arrive at some idea of the probable quantity by means of the following considerations.

There are a good many records of the daily output of fistula bile, and data of this kind have been carefully reviewed by Gamgee (3). The only important observations made since this review are the long and excellent series of experiments of Pfaff and Balch (4). We have summarized their extensive data in Table I.

TABLE I.

Summary of Pfaff and Balch's Experiments.

Group.	Treatment.	Number of Observations.	Average Total Volume of Bile in 24 Hours.	Range.	Average Total Solids.	Range.
1. No medication	—	39	508 c.c.	402–646	1·74	1·60–2·27
2. Medication which had no effect	Salol, corrosive sublimate, calomel	20	497 c.c.	458–543	1·69	1·59–1·76
3. Medication which increased flow of bile	Ox bile, patient's own bile, bile salts	36	628 c.c.	529–787	2·00	1·63–2·84

This work was carried out on a woman, aged 38, on whom a cholecystotomy had been performed sixty-five days previously. During the whole of the experimental period (ninety-seven days) she remained in good health and even gained in weight (14 lb.), although in the opinion of the observers no bile was reaching the intestine.

Group 1 shows the daily output of bile when an ordinary diet was being given—i. e. it represents what we may term the 'normal fistula secretion'.

Group 2 shows the values obtained during the addition to the diet of three supposed cholalogues. It will be seen, however, that they had little, if any, effect, so that in reality this group may be considered as a duplicate of Group 1.

Group 3. Here we see the result of administering dried bile or bile salt. There is a marked increase in the secretion.

In Table II we have collected together observations recorded by various authorities. The better cases, i.e. those whose health was otherwise satisfactory, and in which obstruction was known to be more or less complete, are separated from those in which, from the available evidence, these conditions do not appear so well to have been fulfilled.

From these figures, it would seem that the daily secretion of fistula bile is a fairly constant quantity, which we may take as about 600–700 c.c.

TABLE II.

Amount of Bile (Fistula) secreted in Twenty-four Hours.

(a) *Obstruction complete. Health good. (Cholecystotomy in each case.)*

Date.	Observer.	Number of Experiments.	Average Daily Secretion.	Maximum.	Minimum.
1889	Copeman and Winston (5)	30	780	809	682
1889	Robson (6)	15	852	1122	737
1892	Paton (7)	2	590	680	500
1897	Pfaff and Balch (4)	39	508	646	402
		86	665	1122	402

(b) *Complete obstruction doubtful. Health indifferent.*

Date.	Observer.	Number of Experiments.	Average Daily Secretion.	Maximum.	Minimum.
1883	Yeo and Herroun (8)	8	374	468	327
1891	Paton and Balfour (7)	23	638	814	518
1901	Brand (9)	3	881	1083	694
1902	Austen (10)	6	417	451	378
1910	Bacmeister (11)	14	348	400	200
1912	Menzies (12)	2	470	600	350
		56	435	1083	200

II. *Chemical Composition.*

The chemical composition of bile has been reviewed in considerable detail by Gamgee, Brand, Rosenbloom (13), and Whipple (14), and from their data and from various other sources we have drawn up Tables III, IV, and V, which show the amounts of total solids, cholesterol, and bile salt present in fistula and bladder bile.

TABLE III.

Total Solids and Bile Salts.

(a) *Bladder Bile.*

Date.	Observer.	Number of Observations.	Total Solids.	Bile Salts (Occasional Estimates only).
1845	Frerichs	2	14·4	8·2
1851	Gorup-Besanez	2	14·0	8·3
1874	Trifanowski	2	9·0	2·4
1904	Kimura (15)	33	10·6 (2·7–20·6)	—
1911	Hammersten	2	16·5	9·2
1913	Czyhlarz (16)	3	8·6	3·3
		44	11·0	6·0

TABLE III (*continued*)

(b) *Fistula Bile.*

Date.	Observer.	Number of Observations.	Total Solids.	Bile Salts (Occasional Estimates only).
1873	Jacobsen	2	2·26	1·02
1889	Yeo and Herroun (8)	1	1·28	0·22
1869	Copeman and Winston (5)	1	1·42	0·63
1890	Robson (6)	1	1·80	0·75
1897	Pfaff and Balch (4)	39	1·74	0·57
1899	Zeynek	2	2·64	1·60
1891	Paton and Balfour	2	1·36	0·42
1892	Paton (7)	2	2·30	—
1901	Brand (9)	4	2·12	0·74
1902	Austen (10)	3	1·34	—
1904	Örum (17)	2	2·23	0·70
1911	Hammersten	8	2·44	0·99
1912	Menzies (12)	2	2·25	0·42
1913	Rosenbloom (13)	1	2·98	1·01
1913	Czyhlarz (16)	7	2·02	0·23
		77	1·92	0·715

TABLE IV.

Cholesterol Content.

(a) *Bladder Bile.*

Date.	Observer.	Remarks.		No. of Observations.	% Cholesterol.	Max.	Min.
1912	Peirce (18)	Pathological.	Gravimetric method	23	0·28	1·3	0·01
1913	McNee (19)	Normal.	,,	1	0·16	—	—
		Pregnancy.	,,	5	0·79	1·3	0·64
1913	Czyhlarz (16)	Normal.	Colorimetric method	3	0·52	0·7	0·25
		Pathological.	,,	9	0·53	1·0	0·20
1920	Grigaut (20)	,,	,,	4	0·40	0·81	0·21
1920	Nathan (21)	,,	,,	44	0·33	1·07	0·06
1924	Fox	Normal.	Gravimetric method	3	0·55	0·91	0·29
		Pathological.	,,	8	0·35	0·92	0·04
				100	0·375	1·3	0·01

(b) *Fistula Bile.*

Date.	Observer.	Remarks.		No. of Observations.	% Cholesterol.	Max.	Min.
1910	Bacmeister (11)	4 subjects	Gravimetric method	32	0·043	0·11	0·004
1913	Czyhlarz (16)	,,	Colorimetric method	7	0·050	0·15	0·02
1914	Rothschild	1 subject	,,	8	0·095	0·13	0·07
1820	Nathan (21)	,,	,,	44	0·056	0·08	0·03
1924	Wilensky	,,	,,	20	0·035	0·09	0·03
1924	Fox	,,	Gravimetric method	2	0·042	0·05	0·04
				113	0·057	0·15	0·004

1. *Total solids.* It will be seen that the average value for total solids in bladder bile is about 11 per cent., while for fistula bile it is about 2 per cent.

2. *Cholesterol.* The older analyses often include values for cholesterol, but these are little more than approximations (frequently the crude unsaponifiable matter), because until 1909 no really accurate method was available for the estimation of small amounts of this substance. Since that date there are, however, quite a number of analyses recorded that have been carried out either by the gravimetric or colorimetric methods.

Bladder bile. Selecting those analyses which appeared to be made on fairly normal material, we found the average of 100 determinations to be 0·375, but the range of variation was from 0·01 to 1·3 per cent.

Fistula bile. A marked contrast is seen in the case of fistula bile (Table IV). Here the values are generally about 0·05 per cent., though occasionally they may be considerably higher or lower.

For the sake of comparison several gravimetric estimations of bile cholesterol were carried out upon post-mortem material. The results obtained are to be found in Table V. They show the same wide range of variation about a very similar average figure.

TABLE V.

(a) *Bladder Bile.*

Normal Accident Cases.

Sex.	Age.	Case.	Appearance of Bile.	Cholesterol.
F	51		Yellow. Mobile	0·914
F	5	—	Golden yellow. Mobile	0·451
M	61	—	Dark green. Viscid	0·290
		—	Average	0·552
			Range	0·29–0·91

Hospital Cases.

Sex.	Age.	Case.	Appearance of Bile.	Cholesterol.
M	36	—	Viscid	0·038
M	10	Septicaemia	—	0·090
M	69	Acute peritonitis	Mobile	0·163
M	33	Intestinal obstruction	Dark colour. Mobile	0·375
M	69	Septic endocarditis	Golden brown. Mobile	0·380
M	4	Tuberculosis	Dark. Viscous	0·461
M	1½	,,	Rich yellow. Clear	0·915
			Average	0·346
			Range	0·04–0·92

(b) *Fistula Bile.*

Sex.	Age.	Case.	Appearance of Bile.	Total solids.	Cholesterol.
M	22	Splenectomy, 7 days after operation	Golden yellow	1·46	0·036
		Following day	Rather darker	2·42	0·047
			Average	1·94	0·042

3. *Bile salts.* Up to the present no very satisfactory method for the estimation of the bile salts has been available and the occasional estimations recorded by various observers can only be regarded as approximate.

Examination of the Tables.

1. *Cholesterol.* (*a*) A study of the above data soon convinced us that the cholesterol content of pathological bile did not differ in any marked manner from that found in the more normal material. Both classes showed great variability. We emphasize this point because of the repeated attempts that have been made to correlate the cholesterol content of the bile with that of blood and vice versa. In view of the above, it is not surprising that evidence of this kind has been of a most conflicting character, and there seems little doubt that the differences observed are generally well within the wide range of normal variation. For instance, it does not yet appear to be established that in cholelithiasis there is an abnormal amount of cholesterol in the bile with which the deposits are bathed; nor can we accept the evidence of a higher cholesterol content during pregnancy. Again, while it is no doubt true that anything which causes the accumulation of bile in the blood will raise the cholesterol content, the effect induced is smaller than might at first be expected. Thus the entire suppression of one day's bile output (reckoned from the figures of the fistula cases given above, i. e. 700 c.c. at 0·05 per cent.) would only raise the cholesterol content of five litres of blood from 0·15 to 0·16 per cent. Hence it seems to us that very accurate analyses would be required to detect a failure in the excretion of bile prior to obvious jaundice. On the other hand, it is clear that a high blood cholesterol might be responsible for a considerable increase in the amount eliminated through the bile, without producing a percentage rise outside the range of normal variation.

(*b*) The second point which arises from a study of the foregoing tables is the great variability in composition shown by bladder bile when compared with fistula bile. In searching for an explanation it occurred to us to calculate the ratio of cholesterol : total solids, and this gave the following interesting results:

	Total Solids.	Cholesterol.	Ratio of Cholesterol to Total Solids.
Bladder bile	11·0	0·375	0·034
Fistula bile	1·92	0·057	0·030

We think the substantial agreement between these two ratios clearly suggests that, from the point of view of the cholesterol content, bladder bile differs from fistula bile *only in its degree of concentration.* This result had not been expected, and it reminded us of the statements met with in the text-books concerning the concentrating function of the gall-bladder.

The clearest and most definite statement of this kind, which we have been able to find, is that given by Moore (22) in Schafer's *Text-book of Physiology*, who says:

'As secreted by the liver cells and until it reaches the gall-bladder bile is a clear limpid fluid with a low percentage of total solids and a correspondingly low specific gravity (1010). In the gall-bladder absorption of water takes place, and a mucin-like substance secreted by the epithelia of the gall-bladder is added to it so that it becomes viscid in consistency, the percentage of total solids is much

increased, and the specific gravity rises (1030–1040). According to the time it stands in the gall-bladder these changes become more or less advanced, which accounts for much of the variation observed in the quantitative composition of different specimens of bile.'

No experimental evidence was, however, given in support of this view, and of recent years it had been largely replaced by the hypothesis due to Naunyn (23). This observer was strongly of the opinion that the greater concentration of bladder bile is due to the addition by the bladder epithelia of a second secretion rich in organic matter, mucin, phosphoprotein, and cholesterol.

Brand (9) was one of the first to record any experiments on the question. In support of his belief that the bile is concentrated in the gall-bladder he gives figures showing that this concentration is effected at the expense of the inorganic salts, which, as might be expected, are removed with the water.

In 1922 Rous and McMaster (24) began a lengthy series of experiments upon the nature of the bile secretion which enabled them to demonstrate this function of the gall-bladder.

Working on dogs, they made a considerable number of comparisons between the pigment intensity of the bile as it leaves the liver with its intensity after having remained in the gall-bladder for varying periods. As an average of twelve such experiments they estimated an increased colour intensity equivalent to a concentration of nearly seven times in twenty-four hours. In one or two cases the figures rose to as much as ten times. From these and other investigations they arrived at the conclusion already stated, namely, that the gall-bladder possesses very marked powers of concentrating the bile that enters it from the liver.

2. *Bile salts.* Following out this idea we then calculated a similar ratio for the bile salts. As has already been mentioned, the values obtained for this constituent are probably not nearly so reliable as those for cholesterol, but from our averages we obtained the following figures:

	Total Solids.	Bile Salt.	Ratio of Bile Salt to Total Solids.
Bladder bile	11·0	6·0	0·545
Fistula bile	1·92	0·715	0·372

It would appear from this that the concentration of bile salts in fistula bile is somewhat less than in bladder bile. The explanation which first suggests itself is that this is because in a fistula the bile-salt circulation has been broken and the return of reabsorbed salt rendered impossible. But, as we hope to show later, the output of bile salt in such cases continues undiminished for weeks or even months, and there is no evidence that any reserve supply is being drawn upon. In fact, the real point of interest is not so much that the fistula concentration is somewhat low, but that it is *so high*; while not denying that reabsorbed bile salt may again be excreted into the bile, there seems to us to be little doubt that the liver is not by any means dependent upon this source of supply and that the bile-salt content can well be maintained without it.

Apart from these considerations, however, in view of the fact that the analyses are neither as accurate nor as numerous as could be desired, it is rather questionable whether the difference between these ratios is a real one; and we feel justified in concluding that, as regards bile salt also, the difference between fistula and bladder bile is mainly, if not entirely, one of concentration.

Discussion.

If this view be accepted it will be seen that we are now in a position to calculate the concentrating power of the gall-bladder for the various constituents considered.

TABLE VI.

Concentrated Power of the Gall-bladder.

Constituent.	$\frac{\text{Concentration in Bladder Bile.}}{\text{Concentration in Fistula Bile.}}$	
Total solids	$\frac{11 \cdot 0}{1 \cdot 92} = 5 \cdot 7$	Average 6·87
Cholesterol	$\frac{0 \cdot 375}{0 \cdot 057} = 6 \cdot 6$	
Bile salt	$\frac{6 \cdot 0}{0 \cdot 72} = 8 \cdot 3$	

It will be noticed that the concentration power calculated in this way is of much the same order as that found for dogs by Rous and McMaster (24) using the pigment-intensity method and making direct comparisons between 'liver' and bladder bile.

These comparisons indicate that there would be little difference between bladder bile diluted in accordance with the Rous and McMaster factor and the secretion known as fistula bile. In other words, it would appear that fistula bile is closely similar to normal bile as first secreted by the liver. This was an unexpected conclusion; in fact, when commencing this study, we have assumed that fistula bile must of necessity be an abnormal secretion, more particularly because of the break in the bile-salt circulation. It is of course admitted that we have only dealt with two constituents; whether our conclusions will be borne out by a more complete examination, including mucin, pigment, and inorganic salts, remains to be seen.

An obvious method of testing this hypothesis would be to analyse a number of specimens of 'liver bile' collected as fresh as possible *post mortem*. This we are endeavouring to do by means of a fine glass pipette inserted into the bile-ducts. So far the number of reliable samples obtained in this way have not been numerous enough to justify the drawing of any conclusions, but we are hoping to follow up this side of the question in the near future.

A less satisfactory and more indirect method is that described by Lyon (25), who removed samples of bile from the living subject by means of a duodenal

tube. The ampulla of Vater is first relaxed by the introduction of magnesium sulphate, and the successive fractions removed are differentiated into bile from the ducts, gall-bladder, and finally 'liver bile' itself.

As yet few detailed analyses of bile obtained in this way have been published, but the following figures have been obtained by averaging thirty-seven experiments made by Přibram (1924):

	Total Solids.	Range.	Cholesterol (Colorimetric).	Range.
'Liver bile'	1·75	1·2–2·9	0·05	0·03–0·15

The difficulty of obtaining samples uncontaminated with the intestinal contents by such a method would appear to be considerable, and it is therefore hard to judge how far these experiments can be relied upon, but it will be seen that the values given for total solids and for cholesterol are in good agreement with those obtained in Tables III (b) and IV (b).

The agreement between the cholesterol total solid ratio in fresh and concentrated bile has also another significance, since it can hardly be reconciled with the hypothesis of Naunyn (23) regarding the addition of cholesterol to the secretion after it leaves the liver.

Strictly, this conclusion only applies to normal bile. There is other evidence for supposing that the bile-ducts may be largely responsible for the pathological fluid known as 'white bile', which has been shown to contain cholesterol. (See especially Rous and McMaster (24).)

The figures also negative the interesting suggestion made by Mathews (26) that perhaps the cholesterol content of fistula bile is lower because some may have been diverted to the production of bile acid, required owing to the interruption of the bile-salt circulation.

Amount of Bile Constituents secreted into the Intestine during Twenty-four Hours.

It is of particular interest from the point of view of sterol metabolism to gain some idea of the probable amount of bile constituents reaching the intestine during twenty-four hours. For this purpose we require to know both the composition and total volume of the secretion.

If the above hypothesis is correct, and if we may assume the essential similarity in composition between fistula and liver bile, there still remains a good deal of uncertainty regarding the total daily output of the secretion under normal conditions. Most authorities appear to be inclined to consider it as being equal to, or perhaps rather greater than, that secreted in a case of fistula with complete stoppage; the argument for a somewhat greater secretion being that the bile which has already reached the intestine stimulates the process of secretion itself (see Table I, Group III). On the other hand, there is the suggestion that secretion is unnaturally stimulated in a fistula, owing to the prolonged presence in the intestine of the acid chyme.

We see no means of gauging the relative importance of such opposing factors, and we have therefore made the not altogether improbable assumption that the average fistula volume fairly well represents the normal volume. Such a conclusion is borne out by a study of Table I, which shows that the daily secretion of fistula bile is a very steady process; in fact, it is not easy either to augment or diminish the amount to any appreciable extent. We consider that this is in itself evidence that the mere diversion of the bile has not greatly interfered with the factors concerned in secretion.

Adopting the values already found for the average daily secretion, namely, about 600–700 c.c., we calculate the approximate output into the intestine as follows:

Total solids	= (600–700 c.c.)	× 1·92 %	=	11·5–13 grm.
Cholesterol	= ,,	× 0·057 %	=	0·34–0·4 grm.
Bile salt	= ,,	× 0·72 %	=	4·3–5·0 grm.

We cannot, of course, form any idea of the volume that this quantity of bile will occupy, since that depends entirely upon the amount that undergoes concentration in the gall-bladder. The whole day's secretion, if concentrated seven times (see Table VII), would reduce to a volume of about 100 c.c.

Fate of the Bile Constituents in the Intestine.

1. *Bile salts.* As a result of a number of experiments made by different workers it is generally agreed that the bile salts are reabsorbed during their passage along the intestine. Perhaps the most conclusive evidence for this is the fact that they do not appear in the faeces. Thus Thannhauser (27), who kept two subjects on a known diet for a month and estimated the daily output of bile acid by a modification of Hoppe-Seyler's method, only obtained on an average about 0·4 grm. of cholic acid per diem.

The purpose served by the secretion and reabsorption of bile salt has been the object of considerable investigation, but little information has been obtained except that it is in some way concerned with the digestion and absorption of fat.

In this connexion, however, it is of interest to recall the work of Wieland (1) on the remarkable properties of the bile-acid component, desoxycholic acid, $C_{24}H_{40}O_4$. This body can form intimate mixtures or 'compounds' with a large number of substances, such as the hydrocarbons, fatty acids, cholesterol, &c., and perhaps it is in some such way as this that the fats are 'ferried across the cell membranes'.

2. *Cholesterol.* The position regarding cholesterol is, however, not so clear, being complicated both by the fact that a good deal of sterol is also contributed by the diet, and because of the reduction to coprosterol which takes place under normal conditions in the intestine of the adult.

It has, of course, been repeatedly shown that cholesterol, both free and combined, *can* be absorbed by the intestine, and in their original hypothesis as to its origin and destiny Dorée and Gardner (28) say:

'After the bile has been poured into the intestine in the process of digestion, the cholesterol is reabsorbed, probably in the form of esters, along with the bile salts, and is carried by the blood to its various centres and tissues for reincorporation into the constitution of new cells.'

An examination of human faeces shows that they normally contain considerable amounts of sterol, present in the reduced form known as coprosterol.

In 1921 Gardner and Fox (29), by means of a series of twenty-seven experiments lasting for six days each, found that in healthy adults the amount of coprosterol excreted in this way averaged 0·56 grm. (range 0·27–1·20). This was from 0·2–0·3 grm. more than the amount of sterol eaten with the food. Hence, even had there been no absorption, we require an additional source for the sterol of faeces other than the diet. This source is undoubtedly the bile. Further, the agreement between the calculated amount of cholesterol secreted by the bile into the intestine with that actually obtainable from the faeces is sufficiently close to suggest that in all probability the *bulk of the bile cholesterol is not reabsorbed in the intestine,* but passes directly into the faeces.

Such a conclusion is difficult to reconcile with the well-established power of the intestine to absorb cholesterol from the diet, and it is evident that more work must be done before the matter is cleared up. There are, however, some grounds for supposing that the condition of the intestine, and more especially the amount of cholesterol that becomes reduced to coprosterol, are amongst the determining factors. Apparently it is in just these cases where reduction to coprosterol is least that loss of sterol is at a minimum or does not occur at all. An example of this is found in the case of quite young babies (Fox and Gardner (30)). Again, in the case of the herbivora, whose bile most certainly contains cholesterol, but where no reduction takes place in the gut, there is almost complete sterol reabsorption.

Whether it is true that cholesterol can be better absorbed than coprosterol, there is ample evidence that reabsorption of the former frequently occurs and must surely represent some part in the animal economy.

Origin of the Bile Salts and Bile Cholesterol.

In considering the question of the origin of the bile constituents it seems to us important to recognize that a patient can continue to secrete fistula bile in considerable amount and over long periods without appearing to suffer in health, even although reabsorption is almost, if not entirely, prevented. In support of this statement we quote the following remarkable case recorded by Paton and Balfour (7).

These workers made a series of observations lasting for 100 days on the amount and composition of the bile secreted by a woman with a fistula, whose common bile-duct was said to be completely blocked by a stone. The daily excretion of bile averaged 638 c.c., but in spite of this the patient gradually got well and was eventually discharged. The fistula, however, continued to secrete

bile at the same rate, and, after an interval of *two years*, analyses were again made and yielded similar figures. The patient was now in excellent health, lived an active life, and was able to take an ordinary diet, including fat.

This case is supported by several other equally reliable accounts. Thus Copeman and Winston's patient (see Table II), although secreting an average of 780 c.c. of bile per diem, continued to improve in health over the two months during which the observations were made. Mayo Robson noted even larger secretions (850 c.c.) for this case, which was under observation for fifteen months. Pfaff and Balch's patient (see Table I) was under observation for $5\frac{1}{2}$ months, and, although the daily secretion was 500 c.c., her health improved and she gained in weight.

In all these cases the authors had satisfied themselves that as far as they could tell no bile was entering the intestine, and they therefore inclined to minimize the importance of bile in the digestive processes, looking upon it more in the nature of a waste product excreted by the liver. We may be permitted to doubt whether the obstruction was absolutely complete, since Whipple (14) has shown that the presence of minute fistulae between bladder and intestine occur in fistula dogs and markedly influence their health. But it is perfectly clear that these patients were steadily losing very considerable amounts of cholesterol and bile salt. Thus the daily output of cholesterol would be some 0·5 grm. and that of bile salt at least 2–3 grm.

1. *The origin of cholesterol.* There are at least three possible sources for the bile cholesterol:

(*a*) The view usually accepted is that the cholesterol present in bile originates from the break-down of old blood corpuscles in the liver. We are not aware that any experiments are available that bear directly upon this question, though of course much attention has been paid to the derivation of the pigments. Summarizing an extensive experimental study of the origin of bilirubin, Broun and McMaster (31) state that, while they are satisfied that blood destruction is the sole source of the pigment, the amount excreted is considerably below that which should be produced from the haemoglobin that disappeared from the circulation. They suggest that some pigment conservation is involved. In the case of cholesterol, however, it is interesting to notice that the daily secretion of 0·4 to 0·5 grm. represents the destruction of 250–300 c.c. of blood.

(*b*) We have already referred to the difference of opinion that exists regarding the influence of diet as a factor in the elaboration of bile cholesterol. On the whole, we are not convinced that diet has been shown to have any appreciable effect, and in any case it can scarcely account for the whole supply, since the total intake with the diet has been shown to be less than that excreted with the faeces (Gardner and Fox (29)).

(*c*) *Synthetic origin.* In the paper just referred to we came to the conclusion that there must be some organ in the body capable of synthesizing cholesterol, and it does not seem improbable that this organ may be the liver.

Indeed, several workers, Abelous and Soula (32), Marino (33), Artom (34), Channon (35), claim to have demonstrated that such is the case. We have carefully repeated the experiments of the first two workers, but have been quite unable to confirm either the synthetic or destructive powers which they describe (Gardner and Fox (36)). On the whole, although the mechanism involved is not yet understood, it can hardly be doubted that the organism is able to provide its own supply of cholesterol if necessary. If the supply in the diet is adequate, however, such synthetic activity may not be called into action.

In conclusion, while it is evident that these questions require much fuller investigation, it may well be that all three sources may be involved, in which case the amount of cholesterol that eventually finds its way to the bile will depend upon such factors as the nature of the diet, the amount of blood destruction taking place, and the activity of the synthetic mechanism, if such there be.

2. *Bile-salt.* There is no question of the cholic acid fraction of the bile salts originating directly from the diet, and, as far as we are aware, the only origin that has been suggested is that it may be derived from cholesterol by the removal of the side-chain. The chemical relationship between these two substances is significantly close, and is itself a strong argument in favour of such an hypothesis, but at present we know of no experimental evidence that can be brought forward to support it. If proved, it would greatly strengthen the contention that cholesterol is itself synthesized by the organism, for while the sterol in the diet would approximately cover that excreted in the fistulous bile, it would be altogether insufficient to provide in addition the required amount of cholic acid. So that in any case we are driven to the conclusion that *there must be some organ in the body capable of synthesizing cholic acid.* At present there is no evidence that the group of substances of which cholic acid is a typical representative originates *from* cholesterol, and we suggest that it is therefore more in accordance with the facts to suppose that both are derived by collateral processes from a common origin.

In attempting to explain the above observations, and until further facts are available, we suggest the following working hypothesis:

The liver possesses the power of synthesizing both cholesterol and cholic acid and thus controls the amount of these substances present in the bile. Under normal conditions the amount of cholic acid produced synthetically is probably small, because the bile salts are almost completely reabsorbed from the intestine and return to the liver.

The production and reabsorption of cholesterol is a much more variable process. The liver probably obtains some of its supply from the diet, also from the break-down of old blood corpuscles. Reabsorption hardly occurs at all in some animals, while with others it is practically complete. In the intestine, cholesterol frequently undergoes more or less complete reduction to coprosterol, and this appears to be one of the factors limiting reabsorption.

Conclusions.

1. The daily secretion of fistula bile in cases with complete stoppage averages about 660–700 c.c.

2. The cholesterol content of fistula bile averages 0·06 per cent.; that of normal bladder bile 0·38 per cent. The latter is especially subject to a wide range of variation, which probably accounts for the contradictory conclusions arrived at by those workers who have attempted to correlate the sterol content of bile, blood, and diet.

3. A comparison of the relative cholesterol concentrations in fistula and bladder bile supports the view that concentration of bile is one of the important functions of the gall-bladder. On the basis of the similarity between fistula and 'liver bile', an attempt is made to estimate the amount of bile, bile cholesterol, and bile salt entering the intestine during twenty-four hours.

4. Under normal conditions, bile cholesterol is only absorbed in the intestine to a small extent; there is some evidence that the factor limiting reabsorption is the reduction to coprosterol.

5. The origin of bile cholesterol and cholic acid is discussed and the conclusion arrived at that there must be some organ in the body capable of synthesizing cholic acid; it would seem most probable that both these substances are produced synthetically by collateral processes and from a common origin.

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THE IRON CONTENT OF THE TISSUES IN HAEMOCHROMATOSIS, WITH SPECIAL REFERENCE TO THE BRAIN[1]

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It is well known that haemochromatosis is characterized by the deposition of an iron-containing pigment in the organs, and various investigations, dating back to that of Anschutz (1) in 1899, have shown that this is accompanied by a great increase in the amount of iron contained in the tissues, and is not merely an unmasking of physiological iron already there. These chemical investigations have been directed mainly to the abdominal and thoracic viscera. The bulk of the case reports of this disease are concerned with its naked-eye and microscopic anatomy, covering practically every structure in the body, and compared with this line of investigation the amount of work done in chemical analysis is small. The central nervous system has been almost entirely neglected from both aspects, the only extensive study being that of Herzenberg (7) in 1926, who, however, does not give any analyses showing the actual amount of iron deposited. In the present case an attempt has been made to investigate the amount of iron deposition over as wide a field as possible.

Case Report.

The patient was a man aged 51, who was admitted to hospital in October 1926 on account of general weakness. His previous history was unimportant, except that he had had a cerebral haemorrhage five years before, which had left him with a left-sided hemiplegia. Prior to this he had been a heavy drinker.

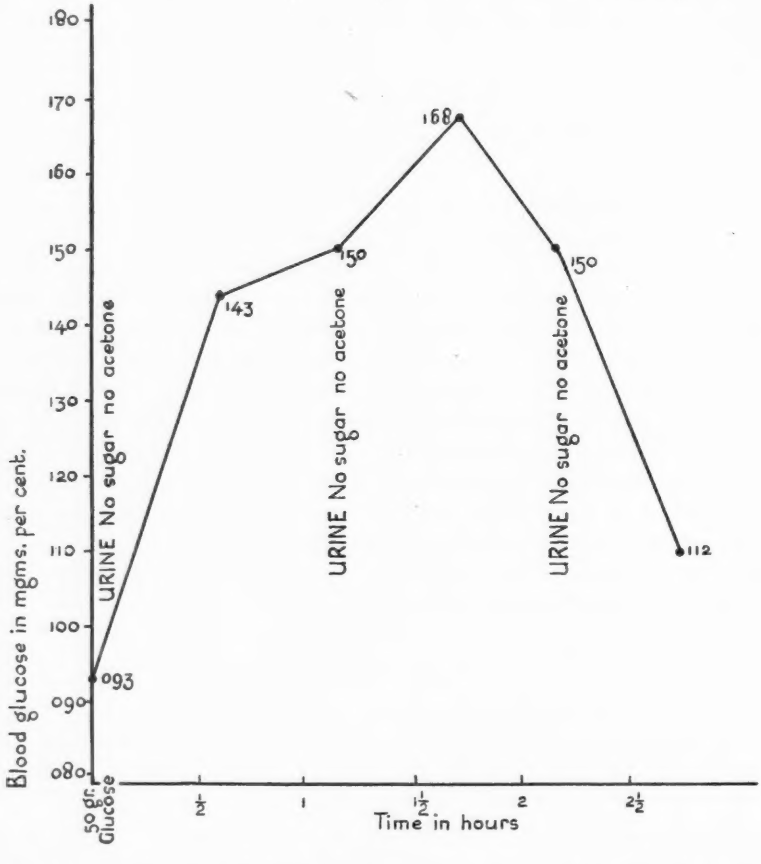
The skin of the face and hands, and to a less extent that of the legs, was of a light bluish-bronze colour, the skin elsewhere being normal. A piece of skin excised from the leg showed a deposit of haemosiderin granules in the corium. During his stay in hospital the pigmentation gradually became deeper, and eventually affected the skin of the back and shoulders as well. The tongue was quite normal, but dark patches of pigmentation appeared on the hard palate. (Pigmentation in the mouth is very unusual in this disease, and has been stated by some authorities never to occur, but it has been described by Blanton and Healy (2 (Case III)).)

Ascites was present, and needed tapping on three occasions, eighteen pints of clear fluid being removed. The liver was hard and nodular, and reached almost to the umbilicus. The spleen was not palpable. Wassermann reaction

[1] Received June 23, 1927.

negative. A blood count (22.11.26) showed red cells 4,500,000 per c.mm.; haemoglobin 90 per cent.; white cells 4,800 per c.mm. The total iron of the blood, estimated by Neumann's method (16), was 0·0506 per cent. Films were stained by the Prussian blue method, but showed nothing abnormal, there being no iron-reacting granules in the white cells.

The urine was consistently normal, there being no glycosuria. In view of the fact that diabetes is such a common event in the terminal stages of haemochromatosis, a blood-sugar curve was done by Dr. S. C. Dyke, and is shown below.



The curve shows a slight departure from the normal, and is of interest in that it represents the beginning of a condition that in time would undoubtedly have developed into true diabetes. It will be noticed that although the figures are not high and there was no glycosuria, the storage mechanism is not perfect. The curve takes 1½ hours to reach its height, and does not drop sharply till 2 hours after the ingestion of the glucose.

The most prominent symptom was intense drowsiness. For the last two months of his life he was in a state of almost continual sleep, from which he could be roused to eat and to answer questions, afterwards relapsing into drowsiness. The condition was quite different from diabetic coma, and it has been noted in this disease by other observers (cf. Troisier (20), Futcher (4),

Garrod (5), Telling (19)). Many terminate in diabetic coma, and somnolence in such could be ascribed to this cause, but the absence of diabetes in the present case indicates that the apathy and sleepiness, which were present to a pathological extent, must be due to the haemochromatosis.

He died on 12.12.26, and a post-mortem was done eighteen hours after death.

Liver. 1,715 grm. This organ had a dense thickening of the capsule on its anterior and upper surfaces, was hard, nodular, and much fibrosed. On section its colour was chrome yellow. Microscopically it showed the characteristic features of an extensive cirrhosis, mainly unilobular, but also invading the lobules. The amount of pigment present was very large, and all of it reacted for iron. All the liver cells contained pigment, mainly in the form of fine granules. The Kupffer cells were prominent and were loaded with masses of pigment granules of larger size. The heaviest deposits occurred in the fibrous tissue bands, as granules filling up the connective-tissue cells and also lying free between the fibres, and as large amorphous clumps of pigment.

Spleen. 275 grm. The capsule was thickened, but the organ was otherwise normal to the eye. Microscopically, there was a slight increase in the amount of fibrous tissue, and an extensive deposit of pigment. This occurred in fine grains in the capsule, and in many of the round cells in the pulp, but the greater part lay in masses in the pulp that were apparently formed by the breaking down of pigment-laden cells. All this pigment reacted for iron, but a non-reacting pigment was found, occurring sparsely in the trabeculae, and particularly affecting the adventitia of the vessels.

Kidneys. 170 grm. each. Normal to the naked eye. Microscopically, there was only a slight amount of pigment found, all of which reacted positively for iron. The glomeruli were quite free, the pigment lying in the cells of the convoluted tubules. There was no increase in fibrosis.

The pancreas was of a deep brown colour, and was firm and much fibrosed. Microscopically, pigment reacting positively for iron was found in the acinar cells as fine granules, the affected cells being irregularly distributed through the organ. It also occurred in the cells of the islets of Langerhans, but to a lesser degree. A few islets were found to be sclerosed, but for the most part they were quite normal. The greatest collection of iron-containing pigment lay in the fibrous tissue bands in the form of large clumps, which were most marked round the periphery of some of the islets of Langerhans. Granules of brown pigment not reacting for iron were found in the connective tissue, and especially in the adventitia of the vessel walls.

The gall-bladder contained a collection of fine pigment stones, but was otherwise normal.

Heart was pulled over to the left by old adhesions, and the muscle was pale and fatty. The valves were normal. The pericardium was adherent, but was not pigmented. The aorta showed slight atheroma, but no pigmentation. Microscopically, pigment granules, all of which reacted positively for iron, were found in many of the muscle fibres of the heart, arranged in a bipolar fashion round the nucleus. There was very little increase in the amount of fibrous tissue.

The trachea was normal, and not pigmented. Both lungs showed extensive adhesions from old pleurisy, but to the naked eye were not abnormally pigmented.

Alimentary canal. Oesophagus and mucous membrane of the stomach were not pigmented. A deep bluish-black pigmentation began suddenly at the pylorus, and continued in the mucous membrane of the intestines and colon, becoming gradually paler, until in the rectum the pigmentation was only just visible. The small intestine was shortened, being only 16 feet long. The peritoneum covering the bowel and the neighbouring part of the mesentery were pigmented, and bluish-black patches of pigmentation occurred on the great omentum. The parietal peritoneum was not pigmented, except where it lay in contact with the

bowel. The peritoneum over the bladder was a slate blue colour, but the mucous membrane of the bladder was normal. Microscopically, no pigment reacting for iron was found, but there was much non-reacting pigment in the muscularis mucosae, and in the gland cells lining the crypts.

The bone-marrow was normal.

The testis was normal to the naked eye, but microscopically, granules of pigment reacting positively for iron were found in the connective tissues of both the testis and the epididymis, particularly in the adventitia of the vessel walls. There was no pigment in the seminiferous tubules.

Lymph glands. The glands at the hilum of the liver and round the head of the pancreas were greatly enlarged, soft, and of a deep rusty colour. The glands at the base of the mesentery and along the iliac vessels were also enlarged, though not to the same extent, and were of a lighter brown colour. Microscopically, a gland from the region of the head of the pancreas showed a general increase in the amount of fibrous tissue. In places the structure of the gland could be made out clearly, although all the cells contained fine granules of pigment. In other places the amount of pigment deposited was so enormous as entirely to obscure all details of structure. All the pigment reacted positively for iron. The iliac glands showed no increased fibrosis and a normal structure. All the cells, however, were loaded almost to bursting point with pigment granules that reacted for iron. These glands evidently represent an earlier stage than that found in the pancreatic gland.

The thyroid gland was small, and deep red in colour. Microscopically, there was a heavy deposit of pigment reacting for iron, occurring almost exclusively in the epithelial cells. In many cells the deposit was so heavy that it obscured all other details, but where the cell was less heavily affected it could be clearly seen that the pigment was first deposited in fine grains along the free, or secreting, side of the cell. The gland was heavily fibrosed, and the vesicles showed great variation in size. There was only a very slight deposit of pigment in the colloid. In the connective tissue and in the adventitia of the vessel walls, cells were met with containing large granules of brown pigment that did not react for iron.

The pituitary was a deep red colour. Microscopically, there was a considerable amount of pigment, all of which reacted for iron. In the posterior lobe it was present in small amount, mainly as fine granules lying free, although an occasional neuroglia cell contained a collection of granules. In the anterior lobe it was much more abundant, and was almost entirely intracellular. All the varieties of cell were affected, but it occurred mainly in the large oxyphil cells. Its distribution was spasmodic, and all gradations occurred from a faint blue stippling of the cell to the deposition of clumps of granules. On the whole the pigment tended to occur round the margin of the cells rather than round the nucleus.

Skin. Microscopically, in the basal cells of the papillae there was a deposit of large brown granules which gave no reaction for iron. Elsewhere all the pigment reacted positively, and there was a very heavy deposit in the connective-tissue cells of the corium, and also as large amorphous clumps of pigment lying apparently free. The deposits were heaviest round the bases of the hair follicles and the sweat glands.

Nearly all the pigment found in the body reacted positively for iron (stained with ferrocyanide of potassium and hot hydrochloric acid), but non-reacting pigment (haemofuscin) occurred, particularly in the vessel walls, the mucous membrane of the intestine, and in the fibrous tissue of the pancreas, spleen, and thyroid, and in the papillae of the skin.

Iron Content of the Tissues.

The amount of iron present was estimated by Neumann's method (16). The tissues are thoroughly washed to free them as far as possible from blood, and then dried to constant weight. In the case of blood, 5 c.c. were ashed direct. Ashing is done in a mixture of boiling nitric and sulphuric acids, and the iron, after precipitation with a mixture of sodium phosphate and zinc sulphate, is separated as the chloride and titrated with thiosulphate against a standard solution of ferric chloride.

TABLE I.

Author.	Percentage of Fe.	Percentage of Haemoglobin.	Red Cell Count.
Present case	0·0506	90	4,500,000
Garrod (5)	0·048	83	4,500,000
	0·056	94	
Howard and Stevens (9)	0·045	100	4,280,000
McClure (11)	0·048	88	5,680,000
Fowler (3)	0·046	—	—
	0·052	—	—
Average	0·049	91	4,740,000

(*a*) *The blood.* The total iron content of the blood in this case was 0·0506 per cent. In Table I are given the corresponding figures from the other cases of haemochromatosis that I have been able to find in the literature, together with the red cell and haemoglobin content of the blood. Fowler (3) found that the average figure for the total iron of the blood in fifteen normal cases was 0·0545. The blood iron in haemochromatosis, therefore, tends to be rather lower than in the normal individual, although it is difficult to say exactly where the deficiency occurs. Fowler distinguishes between the iron contained in the haemoglobin and the rest of the iron, as it is found that blood contains more iron than can be accounted for on the known percentage of this element in haemoglobin. This extra iron he calls the 'difference iron', being the excess of the total iron of the blood over what can be accounted for on Hoppe-Seyler's estimation of the percentage of iron in haemoglobin as 0·42 per cent. Fowler further makes a ratio between this difference iron and the total iron. In a series of fifteen normal cases he obtained figures of 0·0131 for the difference iron with a ratio of 4·2 to 1. In the present case the difference iron amounts to 0·0128 with a ratio of 3·9 to 1. The average figures for the cases given in Table I are 0·011 difference iron with a ratio of 4·4 to 1. The non-haemoglobin iron would thus appear to be lower in haemochromatosis than in the normal, but the available figures are so few in number and the variation from the normal so small that it is not possible to speak with any certainty. It can, however, be safely said that the total iron of the blood in this disease, in marked contrast to the iron of the tissues, is not only not raised in amount, but shows a tendency to be at the lower limits of normal. This implies that haemochromatosis cannot be due merely to a failure

of excretion of iron with accumulation in the body, as has been suggested, for in such a case the level of the blood iron should be raised. The fact that the blood iron is not raised is also against the view put forward by Herzenberg that the iron-containing pigment characteristic of the disease is first formed in the liver, and afterwards carried by the blood to be deposited in the other tissues of the body. Films of blood in the present case were carefully stained for the presence of iron-containing pigment, with negative results.

The low level of the blood iron supports the view that the essential feature of the disease is an abnormal avidity of the tissues for iron.

(*b*) *The tissues.* The amounts of iron found in the various tissues are set out in Table II, expressed as a percentage of the dry weight of the tissue. Where possible, the corresponding figures to be obtained from the literature have been added. Except where otherwise specified, the figures in the normal column are those obtained from control analyses of the organs from a case of chronic interstitial nephritis.

TABLE II.

Tissue.	% of Fe in present case.	Normal % of Fe.	Other Estimations of the % of Fe in Haemochromatosis. Howard and Stevens (9).	Anschutz (1).	Hess and Zurhelle (8).	Muir and Dunn (15).
Liver	3·94	0·08 to 0·18 Hunter (22))	3·09	7·62	7·1	2·38 2·19 5·55 6·43
Pancreas	0·584	0·105	1·439	5·0	—	2·49
Spleen	0·799	0·17	0·46	—	—	0·825
Retroperitoneal lymph glands	(*a*) 14·106 (*b*) 8·55 (*c*) 7·248	0·15	4·2	14·69	—	11·64
Kidney	0·264	0·18	0·484	Trace	—	0·406
Heart	0·329	0·27	—	—	—	0·714
Lung	0·664	—	—	—	—	—
Skin	—	—	—	—	—	0·188
Thyroid	0·406	0·07	—	—	—	—
Testis	0·116	0·103	—	—	—	—
Bone	0·163	0·03	—	—	—	—
Muscle (deltoid)	0·281	0·089	—	—	—	—
Gall-bladder	0·697	0·2	—	—	—	—
Gall-stones	0·127	—	—	—	—	—
Duodenum	0·152	0·08	—	—	—	0·14
Ileum	0·374	—	—	—	—	—
Suprarenal	0·153	0·14	—	—	—	0·121

(*a*) = Glands near head of pancreas. (*b*) = Mesenteric gland. (*c*) = Iliac gland.

There are several features which call for further remark.

1. It will be seen that in every case the amount of iron present in the tissues in haemochromatosis is in excess of the control figure. This is most marked in the case of the lymph glands and the liver, but even the muscles and the bones exhibit the same feature. The bone chosen for analysis was the compact bone of the clavicle, carefully freed from bone-marrow.

2. The amount of iron found in the pancreas is considerably lower than in the other reported cases, and this is probably to be correlated with the absence of diabetes in the present case. Diabetes was present in all the other cases shown in the table. I have not been able to find any analysis of the amount of iron in the pancreas in a similar case to the present one, but it is interesting to note that whereas in this case with 0·55 per cent. of iron there was no glycosuria, in the next highest (1·4 per cent.) glycosuria was present. It is possible that the amount of deposition necessary for the pancreatic function to be so sufficiently damaged as to produce glycosuria may lie somewhere between these figures.

3. As in every other reported case, the retroperitoneal glands contain enormous deposits of iron. While the greatest amount (14·106 per cent.) was found in the glands in the region of the head of the pancreas, both the mesenteric (8·55 per cent.) and the iliac glands (7·24 per cent.) contained a very large amount. It is curious that while the rest of the figures of the present case tend to be lower than in the other cases, the percentage in the lymph glands is almost the highest reported. This great concentration of iron should provide a further means of diagnosis in cases of haemochromatosis, for the abdominal lymph glands, and to a less extent the liver, should be very opaque to X-rays.

4. The deposits in bone and muscle call for attention. In the study of this disease, the deposits in the viscera have attracted most attention, but it would appear from these analyses that the deposition of iron is much more widespread, the muscle containing three times, and the bone five times, the amount found in normal controls. In view of the great extent of these two tissues, the total amount of iron stored in them, in spite of the comparatively low percentage, must be much greater than is generally believed. This question will be dealt with later.

5. The gall-bladder has a percentage of iron of 0·697, which is the highest found in any organ, except for the liver and spleen. Unfortunately the whole of the gall-bladder was used for chemical analysis, so that the microscopic appearances of this deposit are unknown. Presumably this large amount of iron is related in some way with the extensive deposits in the liver. The collection of small pigment stones in the gall-bladder showed an iron percentage of 0·127. I have not been able to attain any control figures for this, but it would appear to be an abnormally high iron content.

6. Except for the content of the retroperitoneal glands, the general level of the figures in the present case is not a high one as compared with the other available figures of this disease. Yet except in the testis and suprarenal (where it is only slightly in excess of the normal control) the amount is in excess of the normal by amounts varying from three times in the case of the muscles to fifty times in the case of the liver, and nearly one hundred times in the retroperitoneal lymph glands. Every tissue examined contained more iron than normal, and it will be shown that this is true also of the central nervous system. Haemochromatosis must therefore be regarded as a very widespread disorder, in which every tissue participates to a greater or lesser degree.

The Central Nervous System.

In investigating the brain and spinal cord, the brain was divided into halves longitudinally. One half was reserved for chemical analysis, and the other half was used for naked-eye and microscopic investigation into the nature of any iron deposit. Pieces of tissue from various localities were first selected for microscopical study, and then, as far as possible, corresponding pieces were taken from the other side for chemical analysis. The region of the internal capsule on the right side was extensively destroyed by the old haemorrhage, the consequent area of softening containing much iron-reacting material. This made the investigation of the region of the basal ganglia much less extensive than would have been desirable.

(*a*) *Chemical analysis.* The brain was analysed for iron by Neumann's method, already referred to. I was unable to obtain any figures from the literature to serve as controls, so the brains of two adult men were also analysed. The results are set out in Table III.

Inasmuch as the amount of iron varies considerably in different areas of the brain, in order to find the average percentage of iron in the brain as a whole, figures have been added for each of the three cases showing (1) the weight of dry tissue analysed and (2) the amount of iron actually present in each instance. By adding these up for each case, a reasonably close approach can be made to the percentage of iron in the central nervous system as a whole. It is found that in the case of haemochromatosis, 19·73 grm. of dried brain from all parts contained 30·401 mg. of iron, giving a percentage of 0·154. In Case A, 21·668 grm. of dry brain contained 11·824 mg. of iron, or a percentage of 0·0545, and in Case B 14·967 grm. of dry brain contained 11·407 mg. of iron, or a percentage of 0·0762. The average percentage for the two control brains is 0·0634. The central nervous system in the present case of haemochromatosis therefore contains 2·4 times as much iron as the normal.

Deiter's nucleus contains less iron than the average of the controls (owing to one of them having a very high figure), and the lateral lobe of the cerebellum contains practically the same amount in all three cases, the factor of excess in the case of haemochromatosis amounting only to 1·2. With these two exceptions, all parts of the central nervous system that have been analysed show individually between two and three times as much iron in the case of haemochromatosis as in the normal. The greatest excess is in the thoracic region of the spinal chord, which shows an excess of 3·7. This relation between the amount of iron normally present in the various areas of the neuraxis and that present in this case suggests that the accumulation of iron has occurred in the cells in connexion with their physiological iron, rather than as a general deposition of iron from some outside source. It is unfortunate that the globus pallidus, which normally contains a relatively large amount of iron, could not be investigated, but the deposition of iron salts resulting from the old haemorrhage made this impossible.

TABLE III.

Region of Brain.	Haemochromatosis. Dry Weight analysed (in Grm.).	Haemochromatosis. Weight of Iron found (in Milli-grams).	Haemochromatosis. % of Fe.	Control Brain A. Dry Weight analysed (in Grm.)	Control Brain A. Amount of Iron found (in Milli-grams).	Control Brain A. % of Fe.	Control Brain B. Dry Weight analysed (in Grm.).	Control Brain B. Amount of Iron found (in Milli-grams).	Control Brain B. % of Fe.	Average % of Fe in the Control Brains.	% of Fe in Haemo-chromatosis ÷ Average % of Fe in Controls.
Lateral lobe of cerebellum	2·614	1·960	0·075	1·925	0·906	0·047	1·481	1·090	0·073	0·060	1.2
Deiter's nucleus	0·256	0·720	0·281	0·392	1·036	0·261	0·211	0·891	0·422	0·341	0·82
Corona radiata	2·025	2·937	0·144	0·767	0·500	0·065	0·989	1·318	0·130	0·097	1·5
Pons	2·082	3·677	0·176	1·448	1·081	0·074	1·497	1·227	0·081	0·077	2·3
Putamen	0·550	2·660	0·483	0·481	1·040	0·216	0·480	0·732	0·151	0·183	2·6
Thoracic chord	0·950	3·130	0·329	0·570	0·509	0·089	—	—	—	0·089	3·7
Occipital lobe	4·530	5·600	0·124	7·615	2·602	0·034	5·857	4·120	0·070	0·052	2·4
Frontal lobe	4·128	5·240	0·126	7·368	3·526	0·047	1·347	0·678	0·050	0·485	2·6
Grey matter (parietal)	1·265	2·159	0·170	0·954	0·750	0·078	1·852	1·760	0·094	0·086	2
Basal ganglia	1·330	2·318	0·174	1·596	0·955	0·059	1·354	0·750	0·055	0·057	3
Total weights	19·730	30·401	—	23·116	12·905	—	15·068	12·566	—	—	—

(*b*) *Macroscopical investigation.* Thin slices of brain were immersed in freshly made 2½ per cent. solution of potassium ferrocyanide for twenty minutes and then transferred to 1 per cent. hydrochloric acid, and left in this solution for a quarter of an hour, the presence of iron being shown by the Prussian blue reaction. A marked blue staining developed in certain areas, particularly the globus pallidus, substantia nigra, dentate nucleus, and the inner layer of the cortical grey matter, but on comparing these findings with the normal brain, no difference was observed in the localities that took up the stain, and the depth of the staining appeared to be the same. The areas concerned coincided entirely with those already described by Spatz (17) as occurring in the normal brain.

(*c*) *Microscopical investigation.* Small pieces of tissue from the different areas were fixed in alcohol, and stained by (1) haematoxylin and eosin; (2) 2 per cent. ferrocyanide of potassium for half an hour, followed by 1 per cent. HCl for a quarter of an hour, and counterstained with basic fuchsin; (3) ammonium sulphide, followed by 1 per cent. HCl and 20 per cent. ferricyanide of potassium (the Turnbull blue reaction); (4) haemalum and van Gieson; (5) basic fuchsin (Mallory (12)) for haemofuchsin.

The sections will be described separately, but it may be said at once that the microscopic appearances showed no salient departure from the normal, except in the case of the choroid plexus.

Choroid plexus. There was a very heavy deposit of pigment, all of which reacted positively for iron. Nearly all the epithelial cells contained a deposit of fine granules. Many of the cells were filled with these, but where the pigmentation was less heavy it could be seen that, as in the case of the thyroid, the deposition occurred first on the free or secreting surface of the cell. Among the epithelial cells larger cells were to be found which presumably belonged to the reticulo-endothelial system, and were packed tight with granules of a larger size than occurred in the epithelial cells. The difference between the two types of cell was quite striking. A small amount of pigment could be found in the fibrous tissue, all of which was contained within the connective-tissue cells. Corpora amylacea were abundant in parts of the section, and some of them exhibited a light diffuse blue staining in their outer regions. There was no apparent increase in the amount of fibrous tissue. In view of the large quantities of iron-containing pigment consistently found in the choroid plexus in haemochromatosis, it is unfortunate that we are entirely ignorant of the iron content of the cerebro-spinal fluid in this disease, although both Wohlwill (21) and Herzenberg (7) suggest that the deposits of iron they found in the brains of their cases were carried there by the fluid.

Medulla. Nothing abnormal seen.

Pons. Nothing abnormal seen.

Olive. An occasional small round cell was seen containing in its cytoplasm a few granules reacting for iron. Otherwise the section was normal.

Dura mater. There was a very scanty deposit of iron-reacting granules in

scattered connective-tissue cells. In the walls of some of the smaller vessels granules were present which did not react for iron, and were presumably haemofuscin granules.

Thalamus. Nothing abnormal seen.

Putamen. A few fine granules which give a positive reaction for iron could be seen in the capillary endothelium in places, and similar fine granules occurred in some of the ganglion cells, but the amount was very scanty.

Frontal lobe. As in the olive, an occasional small round cell was seen containing a few granules of iron pigment, and one branching neuroglia cell was seen studded with rather larger granules giving a positive iron reaction.

Occipital lobe. Nothing abnormal seen.

Internal capsule and globus pallidus. As in the putamen the capillary endothelium in places contained a few fine granules of iron-containing pigment, and similar fine granules occurred in some of the nerve cells.

Deiter's nucleus. Nothing abnormal was met with, but some of the ganglion cells contained occasional pigment granules.

Lateral lobe of the cerebellum. Nothing abnormal seen.

Spinal cord (upper thoracic). Nothing abnormal seen.

Lumbar cord and cauda equina. Nothing abnormal seen.

It will thus be seen that the amount of iron demonstrable microscopically is very small, and bears no relation to the amount of iron actually present in the brain, as shown by chemical analysis. Except for the choroid plexus, there is not the deposition of haemosiderin granules that the chemical findings would lead one to expect. Such iron as is found occurs in a few small round cells, the capillary endothelium in a few places, and to a slight extent in the nerve cells of the globus pallidus and Deiter's nucleus. The findings in no way exceed those described by Spatz (17) as occurring in the normal brain. Other evidence of the condition of the central nervous system in haemochromatosis is very small, and, in particular, there are no quantitative analyses.

Blanton and Healy (2) in a review of the literature state that the brain was examined microscopically in two cases, and that no pigment was found in either. In Case 3 of their series they found a slight incrustation with iron of the connective tissue of the retina and optic nerve.

Wohlwill (21) found in one case that by the macroscopic test for iron all the groups of centres described by Spatz reacted to a degree distinctly in excess of the normal. Microscopically he found fine granules of iron in the glia cells, especially around the vessels, and to a less extent in the vessel walls.

Herzenberg (7) has recently made an extensive microscopic study of the lesions in the brain in two cases. In one case she found deposits of haemosiderin round an area of cerebral softening, the brain elsewhere being normal. In the other case there were extensive perivascular deposits of haemosiderin granules, which in places could be recognized as fine blue points by the naked-eye tests. These occurred in the grey matter of the cortex to some extent, but the pons and mid-brain were the parts particularly affected. In the cortex the deposit

of iron was sharply confined to the capillaries of the grey matter and the neighbouring part of the white matter. In the pons the deposits were very heavy, filling up the perivascular spaces, and in places extending from these into the brain substance, partly as free granules and clumps and partly taken up by the glia cells. The basal ganglia and dentate nucleus, where physiological iron is most abundant, were quite normal. She concludes that the deposits are not due to an increase in the physiological iron, but are derived from the cerebro-spinal fluid as a sort of overflow from the large amounts of iron laid down in the choroid plexus.

Mallory, Parker, and Nye (14) in their paper on the experimental production of haemochromatosis by chronic copper poisoning state that in this disease haemosiderin occurs in the ganglion cells of the central and sympathetic nervous systems, and in combination with haemofuscin in the peripheral nerves. It appears, however, from the rest of the literature that the deposits are generally in relation to the vessels, the nerve cells being unaffected.

Herzenberg's view that the iron found in her cases was derived from the cerebro-spinal fluid cannot be true here, for such iron should be demonstrable by the ordinary microchemical methods, the essential feature of the present case being that there was no such demonstrable excess, although chemical analysis shows an excess of two and a half times the normal. The iron was evidently firmly fixed in the cells in some way that prevented its reacting to the ordinary tests, and it probably represents an increase in the physiological iron normally present. This view receives support from the relation found in nearly every area of the central nervous system between the normal iron and that present in this case.

The essential lesion in haemochromatosis would appear to be some obscure alteration in the metabolism of iron in the tissue cells, as a result of which it accumulates in a form which the cells are unable to excrete. The extent of deposition in the brain here was only a fortieth of that occurring in the liver, and it is quite possible that in such a comparatively early stage of this process, when the excess of iron is not very great, the iron may still be retained in the cell in such a firmly fixed state that it does not give the usual colour reactions. When, as a result of the disordered metabolism, one expression of which is an undoubted avidity of the cells for iron, the excess of iron reaches a certain degree, it may be set free as the characteristic pigment, and then give the colour reactions.

There can be no doubt that the central nervous system is, in common with the rest of the body, subjected to an abnormal deposit of iron in this disease. Wohlwill and Herzenberg have both demonstrated it by the ordinary tests, and though these are negative in this case, the excess is confirmed by chemical analysis. It must be remembered that the figures given in Table II show that the amount of iron laid down in the rest of the body is below what is generally found, and it is quite possible that the results found by these two authors are, like the diabetic phenomena, characteristic of a more advanced stage of the

disease than was present here. Only further quantitative work can clear this point up.

Total iron in the body. This can be estimated with accuracy in those organs where the original weight, the proportion of weight lost in drying, and the percentage of iron in the dry weight are known. The results are set out in the following table:

Liver	16·469	grm.
Lungs	1·328	„
Spleen	0·439	„
Kidneys	0·160	„
Heart	0·230	„
Brain	0·300	„
Total weight	18·926	„

To this figure must be added the amount present in muscle and bone. It is impossible to estimate this with accuracy in the absence of information as to the total weight of each tissue. Keith (10) quotes Macalister for the statement that in a middle-sized man the muscular system weighs 60 lb. and the bony system 20 lb. In the present case the man was of more than middle size, but on that basis the amounts present in these two tissues would be 13 grm. for the muscles and 7 grm. for the bones. While the liver has always been regarded as the most important single reservoir of iron in this disease, the muscles and bones, by reason of their size, store between them quite as much, in spite of their smaller percentage of iron. This brings the total amount of iron up to nearly 39 grm. without taking into account the amounts stored in the lymphatic glands, connective tissues, and other organs. In view of the large amounts present in the abdominal glands, a total estimate of 40 grm. is probably a fair one. The amount present in the tissues of the normal body is somewhere between 2·5 and 3 grm., so that in this case the body contained about fifteen times the normal amount. Muir and Shaw Dunn (15) in their case found 30 grm. in the liver, and estimated the amount in the other tissues at 10 grm., but if the muscles and bones were impregnated with iron the total amount would be greater than that. While the liver undoubtedly provides the single biggest store of iron, its relation to the rest of the iron in the body in this disease is probably much less than three-quarters. In the present case it is two-fifths.

It is interesting to speculate on the length of time 40 grm. would take to accumulate. In health the intake and output of iron always balance, and an excess of iron in the food does not lead to its deposition in the tissues (Gróh (6)). Stockman (18) gives the average intake of iron on an ordinary diet as 10 mg. per diem, while Sherman (quoted by Howard and Stevens (9)) gives it as 12 to 19 mg. If one places it at 20 mg. per diem, and assumes that all the iron is absorbed and none excreted, the time required would be about six years. What little knowledge we have, however, shows that retention is not complete,

a considerable amount being lost in the faeces, though not in the urine. The observations of Garrod (5), Howard and Stevens (9), and McClure (11) all agree that iron is not excreted by the urine in this disease, though normally 0·5 mg. per diem is lost in this way. This absence of urinary iron has probably an intimate connexion with the altered iron metabolism that must occur in the cells. In investigating the faecal iron, Howard and Stevens found that over a period of five days there was a daily retention of only 0·5 mg., or 8·5 per cent. of the amount given (29·3 mg. being given in the food, and 26·8 mg. being recovered from the faeces). McClure in a period of five days, using larger amounts of iron, found a retention of 20 per cent. (0·240 grm. was given in the food and 0·192 recovered from the faeces). On these bases, the times required in the present case would be sixty-four and twenty-seven years respectively. It is impossible to estimate the actual time, but it is quite evident, as was pointed out by Muir and Shaw Dunn, that it is a long one. The disease is extremely chronic in nature, and it is only when it reaches its terminal stages that symptoms are developed which bring it under clinical observation. It is very possible that it may be an inborn error of metabolism, taking forty to fifty years to produce clinical manifestations. This view receives support from the fact that although instances of the fully developed disease are rare, post-mortem evidence would appear to show that the early unrecognized stages are more common. Thus Mallory, Parker, and Nye (14) found haemosiderin cirrhosis in 94 out of 4,507 livers, which they consider represented the early stages of lesions which would have eventually become haemochromatosis. Mallory (13) in a later paper states that in one year, out of 288 post-mortems, 3·4 per cent. showed haemochromatotic changes not suspected during life, although in a similar number in the succeeding year he found none.

Summary.

1. In a moderately advanced case of haemochromatosis, excessive deposits of iron were found in all the tissues examined, except the blood, which contained slightly less than the normal amount.

2. The central nervous system shared in this process, having between two and three times the normal amount of iron. This excess was not demonstrable by the ordinary staining methods. In the cases where it has been so demonstrated, it probably represents a later stage of the same process.

3. The time taken for these deposits to accumulate is very long, and it is possible that the disease is an inborn error of metabolism, the accumulation being so slow that the characteristic clinical symptoms do not appear till middle age is reached.

4. The contrast between the iron content of the tissues and of the blood would seem to indicate that the essential feature of this error of metabolism is an increased avidity of the tissues for iron. The iron slowly accumulates in

the cells in a form which they are incapable of excreting. The pigment originates in the cells, and is not carried to them by the blood-stream from the liver and other places where it is present in exceptional amount.

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NITROGENOUS METABOLISM IN POST-ENCEPHALITIC RIGIDITY [1]

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Preliminary Observations.

REASONS for associating variations in the rate at which endogenous uric acid is produced with variations in the activity of the muscular system were given in a paper by Cathcart, Kennaway, and Leathes (1). The output of uric acid, when the diet contains no compounds of purine bases, is regularly low at night and at its highest in the forenoon (2); it is very strikingly increased as the body temperature rises in fever (3); it is increased when the body is exposed to cold (4), and after vigorous muscular work, though not during its performance. The authors (1) in summing up their inferences from their observations suggest that 'the voluntary muscles are the seat of activities, other than voluntary contractions, which set up metabolic changes that are characterized by an increased output of uric acid, and that some of the most striking variations in the rate at which uric acid is produced in the body are accounted for by these processes and attributable to the muscular system'.

The observations of Spriggs (5) upon the output of uric acid in pathological states involving the muscular system give no support to this suggestion, and he is inclined to locate the origin of endogenous uric acid outside the muscular system.

More knowledge regarding this problem is desirable, and it seemed possible that additional information might be furnished by a study of the uric acid excretion in subjects manifesting Parkinsonian rigidity following epidemic encephalitis. If, as has been suggested, muscular activity other than voluntary contraction influences uric acid production, it was thought possible that the abnormal state of the muscle tone, so marked in some of the cases, might find chemical expression in an altered uric acid metabolism.

This paper comprises the observations made upon five such subjects. The degree of rigidity varied. In one case it was only slight, in three it was moderate, and in one extremely marked.

The subjects were placed upon a diet of adequate caloric value, free from nucleo-protein, creatine, and creatinine, except for the small amount of creatine

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shown by Powis and Raper (6) to be present in milk (0·5 mg. in 100 c.c.) They remained in bed throughout the period of observations. Urine was collected at 7 a.m., noon, 5 and 9 p.m. Special orderlies or nurses were detailed to collect the specimens. This task was greatly facilitated by the patients themselves. The great desire on the part of these unfortunate people to have something done for them made them excellent subjects for investigation, tolerant of dietetic restrictions, and eager to co-operate.

Case I. Male. Aged 22. Wt. 63·2 kg. Post-encephalitic, only slightly rigid. The results are given in Table I.

The diurnal tide in the rate of uric acid excretion is well shown. The nocturnal hourly rate is only 58 per cent. of the rate during the morning hours. The total daily output averages 6·2 mg. per kg. of body-weight, which falls within normal limits, and the uric acid nitrogen forms 1·15 per cent. of the total nitrogen.

For comparison with these, the average figures published for E. L. K. (1) are included. These are figures from a normal man, and the close quantitative approximation of the total uric acid output in the two subjects is striking; the diurnal tide also is similar, the nocturnal rate forming in E. L. K. 55 per cent. of that observed in the morning. It is interesting to note that, whereas Case I remained in bed during the period of observation, E. L. K. carried out the ordinary day's work in the laboratory, and weighed 15 kg. more.

Case II. Male. Aged 24. Wt. 71 kg. Moderate rigidity.

He was catheterized at the end of each period into which the twenty-four hours were divided. The figures are given in Table II.

The results are similar to the normal except at night, when the hourly rate of the uric acid excretion forms only 35 per cent. of the morning rate. The total daily output is 4·96 mg. per kg. of body-weight, and the uric acid nitrogen forms 1·12 per cent. of the total nitrogen.

In addition, creatine appears in the urine during the day, but none is excreted during the night. The amount is not large, in this case only 40 mg. in the twenty-four hours. Creatine is present in the urine of all the other rigid cases examined.

Case III. Female. Aged 28. Wt. 47 kg. Moderate rigidity.

The results are given in Table III.

A normal diurnal tide in the uric acid exists; the nocturnal rate forms 52 per cent. of the morning rate. The total uric acid output is 5·66 mg. per kg. of body-weight, and the uric acid nitrogen forms 1·04 per cent. of the total nitrogen. The creatine excretion of 215 mg. is of a higher order than ever occurs in normal females.

This patient was given 15 minims of tincture of belladonna three times a day, and six weeks later the results included in the lower part of Table III were obtained. The differences are not striking, though the output of both uric acid and creatine is a little less.

Belladonna greatly facilitated the performance of muscular movements, voluntary and reflex (swallowing).

Case IV. Male. Aged 32. Wt. 51 kg.

This subject was so markedly rigid that mastication and swallowing were difficult; the mouth was held partially open most of the time. The bladder could not be emptied voluntarily. Catheterization was necessary.

The results are recorded in Table IV.

A diurnal tide in the uric acid is present. The nocturnal hourly rate is higher than in any of the other cases, and forms 62 per cent. of the morning rate. The total uric acid output is also the highest observed. It is 9·2 mg. per kg. of the body-weight, and the uric acid nitrogen forms 0·88 per cent. of the total nitrogen excretion, which latter showed a negative balance of 3 gr. over the intake.

The creatinuria is more marked than in the other male cases, 106 mg. being excreted daily.

Daily doses of hyoscine were now begun, and as a result voluntary movements were greatly facilitated. Mastication and swallowing were more easily performed, and the bladder emptied naturally. Observations were made after three days of treatment, and also after treatment with hyoscine had been continued one month. The results are shown in Table IV.

The immediate effect of the hyoscine appears to increase for the first three days of observation the uric acid output. It rises from 475 mg. to 552 mg., an increase of 16 per cent. It is now 10·3 mg. per kg. of body-weight, an exceptionally high value for an adult, and the uric acid nitrogen forms 1·1 per cent. of the total nitrogen. The hyoscine was administered at 10.30 a.m. daily. The drug did not produce sleep in this patient.

During the succeeding five hours an increase of nearly 50 per cent. in the hourly rate of uric acid excretion for that period was observed. Both the creatine and creatinine were somewhat decreased. The nitrogen balance was still negative.

One month later, during the whole of which hyoscine treatment had been continued, the uric acid output was reduced to a figure less than before the treatment began. The daily excretion was 7·87 mg. per kg. of body-weight, and the uric acid nitrogen forms 1·03 per cent. of the total nitrogen. The average figures for the day closely resemble the values obtained in Case I. The subject had gained 2 kg. in weight and the nitrogen balance had become positive.

The creatine and creatinine were a little less than before the administration of the hyoscine.

Case V. Male. Aged 35. Wt. 58·6 kg. Moderate rigidity. The results are given in Table V.

The diurnal tide in the uric acid is normal, the nocturnal rate forming 51 per cent. of the morning rate. The uric acid output is 6·83 mg. per kg. of body-weight, and the uric acid nitrogen forms 1·09 per cent. of the total nitrogen. The average daily excretion of creatine is 87 mg.

As in Case IV, he too was placed on daily doses of hyoscine administered at 12 noon. It is to be seen that the effect of the hyoscine is not to influence the total uric acid output for the whole day, but to alter the rate of excretion in the afternoon, so that more was excreted from 5 to 9 p.m. than from 12 to 5 p.m. From 12 to 5 he slept for three or four hours, and the hourly excretion rate fell from 20 to 16 mg.; in the next period it rose from 15·1 to 21·2 mg.

The total creatinine output was diminished, and the greatest diminution in the hourly rate coincided with the fall in the output of uric acid.

Some estimations in Cases IV and V of the uric acid content of the blood in the morning and at night were made to determine whether a demonstrable change in the concentration of the uric acid was associated with the diurnal tide observed in the urine. Folin's method (6) was employed and samples of blood were withdrawn at 10 a.m. and 10 p.m. The results are shown in Tables VI VII, VIII.

The concentration of uric acid in the blood at night is lower than in the morning. The difference is only slight, but it is constant. Rakestraw (9) has obtained changes in the amount of uric acid in the blood after exercise of a much higher order.

Discussion of Results.

It is apparent from these results that the output of uric acid in subjects manifesting moderate degrees of muscular rigidity is within normal limits, whereas in a very rigid case it was abnormally high. In the three moderately rigid cases the output was 5·82 mg. per kg. of body-weight; in the very rigid case it was 9·2 mg., that is to say 58 per cent. higher, and abnormally high for adults.

A 'diurnal tide' in the uric acid excretion occurs in each case. Certain variations in the tides are present. These are shown by the figures in Table IX. In the first column for each period of the day the hourly rates of excretion of uric acid are given, in the second column the hourly rates per kilogram of body-weight. The differences in the tides are more strikingly revealed by the figures expressing rate as a fraction of the body-weight. Thus expressed, certain apparent discrepancies disappear and some important features become accentuated.

In Cases I, III, and V, the decrease in the hourly rate of uric acid excretion in each successive period throughout the day is comparatively uniform.

Case II differs from these in the low nocturnal rate as compared with that observed during the morning hours. In Case IV the total uric acid output is higher than in the other cases, and the rate of excretion during every period is also higher. This difference becomes more apparent when the figures in the second columns of each period are considered. During the first period of the day (7 to 12 noon), uric acid is excreted at a rate of 0·53 mg. per kg. The average of the other four cases in this period is 0·33 mg. The rate is therefore 59 per cent., during the third period 57 per cent., and at night actually 90 per cent. higher than the average from the other four cases. This high value is reduced to 72 per cent. if the low value for Case II is not included in the average for this period.

The rate of uric acid excretion at night in this case is as high as that observed during the morning hours in Cases I, II, and III, when the maximum rate occurs, and almost as high as in Case V. The kidney is capable, therefore, of excreting uric acid at a high rate during the night. (For further evidence on this point see Leathes (2).)

Expressing the rates during the three periods of the day as multiples of the rate at night taken as unity, in Cases I to IV the average values are 2·01, 1·86, and 1·53 respectively; but in Case V they are 1·61, 1·12, and 1·17. The morning rise is marked but not maintained; the output at night being nearly as high as during the hours from noon on.

For comparison with the results in this case, figures selected from the protocols in the paper of Cathcart, Kennaway, and Leathes (1) are included in Table IX. The values for the subject J. B. L. are selected because the uric acid output is higher than in the others, and the test of comparison is accordingly more severe. It will be seen that during February, 1907 (Table VI, p. 442 (1)), the average uric acid excreted daily by this subject was 500 mg. His weight was 70 kg., and the average rates of excretion during the periods in milligrams per kilogram of body-weight are reproduced. The periods do not exactly correspond in time, but

the difference is of no importance in this connexion. It is apparent that in every period the rate of excretion per kilogram is less than in Case IV. The maximum excretion during the month occurred after 470 mg. of sodium urate had been taken. The output of uric acid on that day was 575 mg., an increase of 75 mg. above the average, and even then in mg./kg. body-weight is less than in Case IV, except for one period of the day 0·386 mg. as compared with 0·37 mg. per kg. per hour. During September the uric acid output in the subject (J. B. L.) was higher than at any other time, and on several of the days included in the average, experiments were done specially calculated to increase the uric acid output, so that on some of the days more than 800 mg. were excreted (Table IX, p. 445 (1)). The average daily output was consequently high, 652 mg., and the uric acid coefficient was 9·3, closely corresponding to 9·2 observed in Case IV. This comparison has been given in some detail as it renders more remarkable the high output of Case IV at rest in bed.

In the experiments of Cathcart, Kennaway, and Leathes (1) the ordinary activities of voluntary muscles were found to increase the output of uric acid only in the case of violent exertion; moderate exercise had no effect. In this respect severe rigidity may be compared with violent exertion.

The influence of muscular tension upon the output of uric acid was studied by Leathes and Orr (7). In their experiment, the muscles as far as possible throughout the body were maintained in a state of extreme tension for an hour. After an hour and a half's rest and the usual breakfast, the same condition was maintained for nearly an hour and a half. During the following twenty-four hours the uric acid output was increased 18 per cent. Garry (8) has published figures for the uric acid output under somewhat similar experimental conditions, described as the 'static effort'. He observed a small though definite increase to follow this type of activity, confirming the results of Leathes and Orr (7). His protocols (Table 18) show an increase of 30 mg. in the daily output. The weight of the subject is not given, but in an individual weighing 60 kg. this increase would correspond to 0·5 mg. per kg. After strenuous exercise an increase of 60 mg. was observed, or 1 mg. per kg. Such figures are small as compared with the differences in the uric acid coefficients observed in states of moderate and marked rigidity.

The low nocturnal rate in Case II is both relative and absolute. It was suggested that this might be due to the influence of sleep upon the rigidity. It is difficult to estimate rigidity and more difficult to determine the influence of sleep upon it. The subjects investigated by us slept lightly, and attempts at examination usually awakened them. However, all who examined Case II during sleep agreed that resistance to passive movements of the arms was less during sleep than when the subject was awake. In Case IV, a poor sleeper, no such difference could be detected; in the other cases rigidity was perhaps somewhat diminished during sleep, though not so much as in Case II.

The action of hyoscine is interesting. Its effects were most marked in the very rigid case. For the first three days the output of uric acid was increased in

each period of the day, but most in the five hours immediately following the dose. No sleep was induced by the drug. On the fourth day these initial effects disappeared, and subsequently (one month, eight months, and fourteen months later), so long as the drug was administered, the daily output was diminished nearly 20 per cent. In the less rigid Case V sleep was produced by hyoscine, and during this sleep the output of uric acid fell, rising again, however, during the subsequent period, so that the total output for the day remained unchanged.

This action of hyoscine is obscure. Its beneficial effects in Case IV were striking; rigidity persisted in marked degree, but both voluntary and reflex movements were greatly facilitated. These effects were striking within twenty-four hours of the first dose. Just at first the uric acid output was increased, but subsequently so long as the drug was given it was considerably diminished (see Table VII after eight months' treatment, and similar figures again were obtained six months later).

Even, however, when reduced by hyoscine the output in this, the most rigid case examined, was higher than in any of the others.

Conclusions.

1. Moderate degrees of post-encephalitic rigidity may be accompanied by a normal output of uric acid in respect of both the total for the day and the diurnal tide.
2. A case of severe rigidity showed both a high total for the day and relatively high output at night.
3. In this case the diminished rigidity effected by hyoscine was accompanied by diminished total output and a more normal difference between that at night and in the morning.
4. Creatine is excreted by all cases of post-encephalitic rigidity that have been examined.

It is a pleasure to record our thanks to Professor Hall, who provided cases for investigation and in innumerable ways manifested a great practical interest in this part of the investigations on epidemic encephalitis; to Dr. Vincent and Dr. Matheison of the South Yorkshire Mental Asylum for indispensable co-operation in the study of two cases; and to Professor Leathes for interest and advice.

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TABLE I.

Case I. Aged 22 years. Wt. 63·2 kg. Slightly rigid.

Date.	7 a.m.–12 noon.				12 noon–5 p.m.				5–9 p.m.				9 p.m.–7 a.m.				Total in 24 Hours.				Uric Acid Co-efficient.
	N.	U.	C.	V.	N.	U.	C.	V.	N.	U.	C.	V.	N.	U.	C.	V.	N.	U.	C.	V.	
31.3.26	704	13·8	72	41	767	22·4	73	81	603	17·6	56	40	414	12·7	51	22	14	0·381	1·46	997	
5.4.26	588	24·9	79	37	528	18·7	67	32	504	15·6	62	28	354	13	51	18	11	0·400	1·46	627	
6.4.26	636	23·5	106	103	657	16	73	122	597	16·1	78	48	321	10·6	51	19	12·1	0·372	1·74	1537	
7.4.26	476	17·2	77	48	508	18·3	65	51	515	16·4	65·5	41	353	12·4	54	28	10·6	0·364	1·485	948	
8.4.26	536	27·9	104	109	316	12·5	48	54	557	14·95	74	40	360	12·1	57	23	10·4	0·397	1·63	1263	
9.4.96	380	18·8	50	35	574	22·4	72	66	363	13·3	49	25	328	12·3	50	24	9·34	0·372	1·28	801	
11.4.26	701	26·4	69·8	134	668	25·8	68	126	527	13·7	45	47	387	14·5	54	24	12·7	0·457	1·39	1725	
12.4.26	566	19·1	67	50	592	21·8	68	89	559	18·2	110	36	318	12·2	30	17	11·3	0·400	1·43	1024	
Average	573	21·45	78·1	69·6	576	19·74	66·75	77·6	528	15·7	67·4	38·1	353	12·5	49·7	22	11·4	0·393	1·484	1115	6·2

N = total nitrogen in mg. per hour. U = uric acid in mg. per hour. C = creatinine in mg. per hour.
V = volume of urine in c.c. per hour. Totals expressed in grammes.

TABLE II.

Case II. Aged 24 years. Wt. 71 kg. Moderate rigidity.

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 Hours.					Uric Acid Co-efficient.
1926.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	
May 2	427	20	63·1	—	31	564	19·8	64	5·7	102	457	18·6	56	7·2	47	317	7·9	47·7	—	24·4	9·79	0·348	1·3	0·057	1088	
3	531	22	68·6	2·4	108	432	19·4	61	—	44	529	16·3	59·7	5·1	45	379	7·5	52	—	46	10·87	0·356	1·42	0·034	1439	
4	435	21·2	61	—	36·4	516	19·7	60	—	33	566	14·8	41·7	—	31·5	282	9·3	52	—	69·3	9·9	0·361	1·31	—	1155	
6	434	20·4	59	5·2	41·3	485	18·9	59	6	41	512	13·8	57	—	32	394	7·3	51	—	33·2	10·5	0·326	1·33	0·058	866	
7	423	22·8	59	4	57·6	614	21·7	59	3·7	47·6	566	17	61·5	3	60·5	357	7	43·5	—	34·7	11·05	0·369	1·28	0·051	1126	
Average	450	21·20	62·2	2·3	54·9	522	19·9	60·6	3·1	53·5	526	16·1	55·2	3·1	43·2	345·8	7·8	49·2	—	41·5	10·42	0·352	1·33	0·040	1135	4·96

N, U, V as in Table I. C I = creatinine mg. per hour. C II = creatine mg. per hour.

TABLE III.

Case III. Aged 28 years. Wt. 47 kg. Moderate rigidity.

Date.	7 a.m.-12 noon.					12 noon–5 p.m.					5-9 p.m.					9 p.m.-7 a.m.					Total in 24 hours.					Uric Acid Co-efficient.
1926.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	
May 10	502	17·3	36·1	14·7	55·6	460	13·3	40·3	13·6	62·4	398	5·6	34	8·7	23·5	450	7·1	41·4	6·1	20·5	10·9	0·246	0·933	0·237	889	
11	425	15	36	12	56·4	382	13	38·5	10·3	31	280	10·6	29·5	7·4	16	296	9·6	38·5	1·4	13·9	8·12	0·288	0·876	0·157	640	
12	479	16·6	36·4	17·5	54	558	17·7	48·4	9·3	73	470	11·7	37·5	8·7	41·5	303	6·1	35·9	8·3	18·5	10·1	0·278	0·933	0·250	984	
13	478	16·2	42	10·9	97	307	11	38·8	6·3	50	302	10·3	58·8	14·9	41	242	6·8	32·8	6·1	22·9	7·55	0·245	0·968	0·207	1128	
14	328	13·3	34·3	12·9	75	280	13	35·9	10·2	21	434	18·4	42·9	14·5	36	310	8·3	38	5	18·8	7·88	0·288	0·903	0·224	812	
15	382	16·3	36·9	10·4	36	338	12·8	33·6	7·1	22·6	395	12·6	40	12·4	20	356	9·6	39	10·3	21·4	7·93	0·273	0·824	0·220	586	
16	377	9·1	19·1	9	18·6	366	13·1	45	9·6	62	329	15·4	44·5	6·5	19·8	266	7·3	24	12·7	13·8	8·45	0·229	0·775	0·264	620	
17	451	16·5	44·9	8·1	104	294	15	41·4	7	27·4	312	11·2	23·5	8·8	19	289	8·2	38·1	5·1	18·9	7·86	0·284	0·907	0·162	921	
Average	428	15·2	35·7	11·94	50·4	373	13·6	40·2	9·2	43·7	365	12	33·8	10·2	27·1	314	7·9	36	6·9	18·6	8·6	0·267	0·890	0·215	823	5·67
July 1	453	11·7	33·9	7·2	85·5	316	11·7	33·3	4·4	44·8	397	7·9	35	—	61·5	450	7·3	41·8	4·7	51·6	9·93	0·222	0·893	0·105	1283	
2	488	16·8	38·1	8·8	72·4	292	7·7	31	4·3	57·8	587	9·2	48·8	9·1	125	363	9	34·5	6·1	34·4	9·87	0·249	0·885	0·163	1494	
Average	470	14·2	36	8	79	304	9·7	32·1	4·3	51·3	492	8·5	46·9	4·5	93·2	406	8·1	38·2	5·4	43	9·90	0·236	0·889	0·134	1389	5

N, U, C I, C II, and V as in Table II.

TABLE IV.

Case IV. Aged 32 years. Wt. 51 kg. Extreme rigidity.

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Uric Acid Co-efficient.
1926	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	
May 24	878	24·8	64	4·6	79·2	734	17·7	53·6	3·7	52·6	781	20	57	6·1	47·3	722	16·6	56·8	4·5	43·3	18·4	0·459	1·385	0·110	1281	
25	845	29·8	63·5	5	85·6	770	20	56·5	4·5	54·8	804	18·5	54	9·7	41·8	657	16·9	53	3	37	17·9	0·492	1·346	0·115	1239	
26	885	26·8	69	5·4	77·4	670	18·3	50·3	6·7	48·4	805	20·5	58·5	4·2	45	600	16·8	47·9	1·7	34·7	17	0·475	1·310	0·094	1156	
Average	869	27·1	65·5	5	80·7	724	18·7	53·5	5	51·9	797	19·7	56·5	6·7	44·7	660	16·8	52·6	3·1	38·3	17·8	0·475	1·347	0·106	1225	9·2
May 30	924	28	57	5·5	53·4	750	28	56·7	—	46·8	854	24·7	58	4·6	49·5	580	19·2	48·3	4·2	36	17·6	0·571	1·283	0·083	1059	
31	679	26·8	49·7	3·4	66	862	29	66·5	4·2	63	555	17·6	41	—	35	681	18·2	51·8	3·2	40·8	16·64	0·530	1·260	0·069	1162	
June 1	799	23·5	59	2·4	86·3	789	26	58	3	55·4	719	22·4	57	3	44	524	21·3	53	4	34·3	16·10	0·556	1·340	0·092	1211	
Average	801	26·1	55·2	3·8	68·6	800	27·7	60·4	2·4	55·1	709	21·6	51·7	2·5	42·8	595	19·6	51	3·8	37	16·78	0·552	1·294	0·081	1144	10·37
June 2	685	28·2	56	—	57	615	21	56	—	37	642	16·3	51·5	6	35	594	16·2	53·2	2·7	68	15	0·473	1·300	0·050	1298	
28	650	25·6	57	4·1	93·4	550	16·14	52·4	2·6	51·6	566	15·5	51·2	3·36	44	441	13·1	48·1	1·15	33·1	12·67	0·402	1·230	0·058	1232	
29	563	22·3	54	3·9	60·6	810	29	81	11·4	68	435	11·6	43	3·7	28	432	13·5	47	1·5	65·2	12·92	0·438	1·310	0·106	1109	
30	562	22·3	73	2·7	50	478	15	47·6	2·6	32	595	16·25	50·4	4·5	39	415	11·93	41·5	2	27·2	11·73	0·371	1·220	0·064	837	
Average	592	23·4	61·3	3·6	68	613	20·1	60·3	5·5	50·5	532	14·45	48·2	3·85	34	429	12·84	45·5	1·55	41·8	12·44	0·404	1·250	0·076	1059	7·8

May 27, hyoscine $\frac{1}{150}$ gr. N, U, C I, C II, and V as in Table II.

TABLE V.

Case V. Aged 35 years. Wt. 58·6 kg. Moderate rigidity.

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Uric Acid Coefficient.
1926	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	
June 4	424	17·8	43	5·9	27	624	21·1	62	6·4	34·6	441	13·9	91	—	25·5	402	11·9	54·8	—	18·1	11·01	0·369	1·44	0·062	591	
6	698	23·2	67·6	—	39	800	19·2	85	4·9	30·2	538	16	57	1·8	26·2	306	9·4	41·5	—	14·5	12·71	0·370	1·40	0·032	596	
7	661	23·2	67	6·3	51	485	16·2	55	8	29	539	10·7	57	—	15	402	13·1	45	5·9	24·5	11·64	0·376	1·27	0·131	702	
8	499	15·4	50	4·7	60	594	18	58	—	39·4	529	12·8	53	4·7	27	334	9·7	41·7	3·6	16·1	10·92	0·313	1·17	0·078	766	
9	539	21	54·4	3·3	44	463	14·7	48·4	2·5	50	461	14·9	53	3·3	50	351	11·7	51·8	1·3	25	10·36	0·355	1·24	0·055	920	Starvation
10	654	15·6	59·8	5	89	834	23·9	74	7·5	61·4	678	16·7	59·8	3·4	38·2	412	14·2	55	—	19·5	14·28	0·406	1·46	0·076	1099	
11	616	23·6	62	6·5	63	592	21·6	66·6	—	37·6	505	16·2	51	—	29·5	488	17·5	63·1	—	23·1	12·94	0·466	1·48	0·033	851	
13	720	26·5	67	4	64·6	840	21·6	85·8	13·7	46·4	552	17·9	54	7·2	31	377	14·9	42·4	7·7	18·9	13·78	0·461	1·40	0·194	868	
14	560	26·4	53·8	7·8	40·2	560	23·4	52·2	9·6	37·8	495	16·9	45	8·1	28·3	363	11·9	45·8	—	17·9	11·20	0·435	1·17	0·119	682	
Average	579	21·4	58·3	4·8	53·1	644	20	65·2	5·8	40·7	526	15·1	57·9	3·2	30·1	382	12·7	44·6	2·1	19·7	12·10	0·395	1·34	0·087	786	6·83
15	578	22·8	50	3·5	48·4	464	13·4	50	7·9	25	600	17·4	55	9·8	33·2	445	13	46·7	5·3	24·3	12·06	0·380	1·19	0·149	743	
16	395	15·4	36	7·7	41	488	15·4	49	5·8	37	700	20·95	65	—	45	399	9·9	36·8	5·2	23·1	11·19	0·326	1·05	0·120	801	
17	590	10·3	29·9	5·9	57	454	14·2	44	6·4	48	770	32·4	101	9·4	110	450	13·8	50·2	3·5	30·1	12·60	0·389	1·27	0·129	1266	
18	510	21	43·6	6	53	432	18·4	50·6	3·4	42	518	15·9	49	6·2	35	478	14·4	50	5·4	30	11·56	0·405	1·17	0·125	914	
20	702	22·4	62·4	2·9	72·6	572	19·2	59	4·4	44	644	22·5	49	1·4	43·5	402	13	43·6	2·6	30·8	12·97	0·428	1·28	0·068	1066	
21	607	26·6	59	5·8	53	382	12	44	1·4	25	646	19	58	8·6	36·2	407	12·6	40	4·5	27·3	11·61	0·395	1·15	0·115	807	
22	745	25·7	66·4	5·2	64·4	545	19·3	57·6	8·1	35	624	20·5	59·5	6·3	35·2	340	11·2	36·4	1·5	20	12·35	0·419	1·22	0·107	838	
Average	590	20·6	49·6	5·3	55·6	477	16	50·6	5·3	36·5	643	21·2	62·3	6	48·3	417	12·6	43·4	4	26·5	12	0·392	1·19	0·116	919	6·83

N, U, C I, C II, and V as in Table II. Hyoscine $\frac{1}{150}$ gr. June 15.

TABLE VI.

Case IV.

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Blood Uric Acid.
	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	
2.2.27	635	24·5	67	6·5	52	561	16·8	54·3	8·7	47·4	625	18·9	59·5	4·9	41	477	13·4	51	4·9	28·4	13·3	0·416	1·35	0·144	944	
3.2.27	676	23·1	62	6	55	591	17·8	59	5·3	44	672	15·3	55·5	7	35	488	10·6	53	3·4	23·9	13·9	0·371	1·36	0·118	874	1·466 10 a.m. 1·136 10 p.m.
4.2.27	641	23·7	59	8	37	656	19	59	7	33	694	15·5	56	2·7	36	517	13·8	53	3·5	23·8	14·4	0·413	1·35	0·122	733	1·538 10 a.m. 1·42 10 p.m.
5.2.27	—	31·5	—	—	48	—	14·5	—	—	32	—	15·3	—	—	53	—	11·7	—	—	24·6	—	0·407	—	—	857	
6.2.27	540	22·6	56	2·2	42	495	15	54	6	27·6	578	18·9	57	5·4	32	471	12·9	50	4·7	24·4	12·2	0·390	1·28	0·109	721	
7.2.27	644	23	57	4	52	544	15	57	6·4	28	593	17·7	55·5	9·5	30	446	14·6	49	3	24·5	12·8	0·407	1·29	0·120	767	1·60 10 a.m. 1·32 10 p.m.
8.2.27	468	23·1	56·4	6	32	468	23·1	56·4	6	32	637	18·5	56	4·5	41	497	13·4	51	5	26·9	12·2	0·439	1·30	0·128	754	1·88 10 a.m. 1·588 10 p.m.
Average	601	24·5	59·5	5·5	45	553	17·2	56·6	6·6	35	633	17·1	56·6	5·7	38·3	483	13	51	4·1	25	13·1	0·406	1·32	0·123	807	

N, U, C I, C II, V, as in Table II.

TABLE VII.

Case V.

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Blood Uric Acid.
	N.	U.	C I	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I	C II.	V.	N.	U.	C I.	C II.	V.	
21.1.27	524	19·2	53	10	55	461	13·7	48	10·0	36·6	353	12	41	6	25	369	12·4	45	6	24	10·0	0·337	1·12	0·186	797	
22.1.27	940	36·3	102	10	72·6	601	23·4	72	9·4	37·2	360	11	42	3	19·2	466	14·9	57·9	2	23	13·8	0·491	1·60	0·127	857	
23.1.27	481	17·2	53	6·7	29·2	624	21·4	67·4	7·6	32	695	18·9	72	2·5	35	564	15·3	56·3	1·9	33	13·9	0·422	1·45	0·101	776	
24.1.27	398	12·6	39	3·5	36·6	581	19	59	6	46	464	14·1	45	3	31	616	21·4	66·4	4·7	40	12·9	0·426	1·33	0·106	938	1·488 10 a.m.
																										1·366 10 p.m.
25.1.27	319	12	35	4	38·6	586	21	71	12	53	587	20·1	75	9·5	47	495	18·4	59	5·6	29	11·8	0·427	1·42	0·173	936	
26.1.27	291	8·6	29·6	2	31	469	16	58	4·6	37	738	23·1	85	10	50·5	430	17·6	54	6·6	27·8	11·1	0·390	1·32	0·140	820	1·80 10 a.m.
27.1.27	348	13·5	48	3	43	569	19	66	8	41	699	21	79	10·5	48	382	13·3	48	3·9	25·5	11·21	0·377	1·37	0·134	867	1·726 10 a.m.
																										1·618 10 p m.
28.1.27	—	19	—	—	49	—	17·3	—	—	32	—	27	—	—	54	—	14·1	—	—	22	—	0·430	—	—	841	
*29.1.27	—	4·4	—	—	20	—	27	—	—	72	—	8·	—	—	16·5	—	21·8	—	—	45	—	0·410	—	—	1028	
*30.1.27	236	6·4	19	1·4	21	751	26	79·5	7·9	59	817	24	34	—	51	430	14·4	50·4	1	25·5	12·5	0·400	1·34	0·057	859	
31.1.27	552	24	60	3	51	390	13	49	4	24·4	510	13·1	58	3·4	27	390	11·1	43·5	1·6	19·8	10·7	0·351	1·21	0·065	683	1·928 10 a.m.
																										1·552 10 p.m.
Average	454	15·7	48·8	4·8	40·6	559	19·7	63	7·6	43	580	17·5	65	5·3	37	460	15·9	53·4	3·7	28·6	11·99	0·405	1·35	0·121	855	

N, U, C I, C II, and V as in Table II.

* The low values during the 7 a.m.–12 noon period are attributed to incomplete evacuation of the bladder, as it was emptied with difficulty at midday.

TABLE VIII.

Case IV.

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Blood Uric Acid.
	N.	U.	C I	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	1·648 10 p.m.
12.2.26	456	10·4	33	2·9	85	472	10·5	43	3·3	40	425	9·1	41	2	27	294	6·8	35·6	5·5	15	9·28	0·210	0·900	0·095	887	1·97 10 a.m.
																										1·654 10 p.m.
13.2.26	634	14	41	4	96	560	10·8	45	4·7	58	427	5·5	34	2·7	31	356	6	37	6·7	18	11·24	0·206	0·940	0·120	1076	
14.2.26	546	14	39	2·1	53	479	12	40	2	31	172	2·3	17	1	10	339	6	32·4	2	15·2	9·2	0·200	0·790	0·042	614	2·174 10 a.m.
																										1·802 10 p.m.
15.2.26	544	13·5	44	2·4	31	474	10	38	4·2	26	430	8·1	37	3·1	19	329	6·9	35·3	2·5	13·3	10·1	0·219	0·920	0·070	495	Hyoscine $\frac{1}{150}$
16.2.26	502	14·5	41	1·8	23	611	14	42	6	38	408	10·5	33	4	19·5	362	8	36·6	3·5	14	10·8	0·262	0·913	0·090	525	
17.2.26	508	14·4	45	4·8	27	508	14·4	45	4·8	27	508	14·4	45	4·8	27	302	4	36·4	2·9	12·5	9·12	0·213	0·900	0·086	446	2·068 10 a.m.
																										1·858 10 p.m.
Average	488	12·5	37·4	2·5	47	508	11·1	42	4	45	405	9·3	36	2·4	24·4	335	6·7	36	3·7	16	9·83	0·220	0·892	0·078	711	

N, U, C I, C II, and V as in Table II.

TABLE IX.

Rates of Uric Acid Excretion.

	7 a.m.–12 noon.			12 noon–5 p.m.			5–9 p.m.			9 p.m.–7 a.m.			Uric Acid Coefficient.
	Mg. per Hour.	Mg. per Kg. per Hour.	D/N.	Mg. per Hour.	Mg. per Kg. per Hour.	D/N.	Mg. per Hour.	Mg. per Kg. per Hour.	D/N.	Mg. per Hour.	Mg. per Kg. per Hour.	D/N.	
Case I	21·45	0·34	1·73	19·74	0·31	1·58	15·7	0·25	1·26	12·5	0·20	1·0	6·2
Case II	21·2	0·30	2·75	19·9	0·28	2·56	16·1	0·23	2·07	7·8	0·11	1·0	4·96
Case III	15·2	0·32	1·92	13·6	0·29	1·72	12·0	0·255	1·52	7·9	0·17	1·0	5·66
Case V	21·4	0·365	1·68	20·0	0·34	1·57	15·1	0·26	1·29	12·7	0·22	1·0	6·83
Case IV	**27·1**	**0·53**	**1·61**	**18·7**	**0·37**	**1·12**	**19·7**	**0·39**	**1·17**	**16·8**	**0·33**	**1·0**	**9·2**
J. B. L. Feb.	26·0	0·371	1·53	23·0	0·328	1·35	19·0	0·271	1·1	17·0	0·232	1·0	7·1
J. B. L. (Na urate)	28·0	0·40	1·56	27·0	0·386	1·50	17·0	0·243	0·945	18·0	0·257	1·0	8·2
J. B. L. Sept.	39·0	0·56	1·96	34·0	0·485	1·71	28·0	0·40	1·41	19·9	0·284	1·0	9·3

D/N = Diurnal rate expressed as multiple of nocturnal rate taken as unity.

THE ACTION OF DIGITALIS IN CARDIAC FAILURE WITH NORMAL RHYTHM[1]

By JOHN HAY, H. WALLACE JONES, AND PHOEBE INCE[2]

With Plates 7 and 8

Introduction.

'THAT digitalis has a power over the motion of the heart to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends', was observed by Withering in 1785 after a careful study of the action of the drug extending over a period of ten years. It is significant that, while chiefly concerned with the diuretic effects of the foxglove, he was able to predict with certainty that 'if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcous limbs readily pitting under the pressure of the finger, we may expect the diuretic effects to follow in a kindly manner'; his observations thus coinciding with the opinion held to-day that the type of case in which digitalis acts with most certainty is that of cardiac failure with auricular fibrillation and general oedema.

The position with regard to the action, if any, of digitalis on hearts failing with normal rhythm is still somewhat obscure.

Lewis (1) regards 'the reduction of accelerated ventricular action as the only important action of the drug upon the human heart of which we have knowledge; that there are few, if any, instances of which we know the certainty in which digitalis acts beneficially, except cases of accelerated action; there are few instances of acceleration in which the drug produces unquestionable benefit apart from those provoked by fibrillation of the auricles'.

Mackenzie (2) also considers the action of the drug in slowing the heart and improving the patient's condition to be almost entirely limited to the class of patient showing auricular fibrillation. Occasionally there is remarkable slowing where there is a normal rhythm, but these cases are, in his experience, rare. He lays down as a law 'that so far as slowing of the heart is concerned, the action of digitalis is far less effective when the rhythm of the heart is normal than where there is fibrillation of the auricles'.

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Other observers, on the contrary, find that with normal rhythm, slowing of the heart-rate by digitalis may confidently be expected in those cases where failure is associated with a rapid heart-rate and marked oedema (3, 4, 5).

In non-fibrillating hearts where a marked fall does occur from a previously rapid rate, Cushny (6) states that the pulse-rate never reaches the 40 or 50 per minute which sometimes occurs in auricular fibrillation. Sutherland (7) noticed an almost invariable marked fall in heart-rate in children with rheumatic hearts and normal rhythm, and claims that 'this action is as specific as in the case of the treatment of auricular fibrillation, and the beneficial effects are as striking'.

Some regard the slowing of the heart in normal rhythm as evidence of digitalis intoxication (8). Cohn and Fraser (9) in a series of cases found slowing of the heart occurred in only one patient before the onset of digitalis symptoms, and in five more afterwards.

It appears, however, that the influence of digitalis on the failing heart with normal rhythm is by no means confined to its action on the heart-rate. 'Slowing of the pulse, when elicited, bears no relation to the effects on the general symptoms: oedema disappears, dyspnoea is relieved, often without any change in rate; while in others the pulse shows a distinct fall, but no improvement, either subjective or objective, occurs' (10).

The effect on the heart-rate being thus an inconstant factor, other influences of the drug must be sought to account for the subjective and objective changes which occur as a result of the exhibition of digitalis.

The effect on heart-muscle. That certain changes in the electrocardiogram occur during the course of digitalis administration is regarded as definite evidence that the drug acts directly on the heart-muscle. The changes observed are: A. *Effect on conduction*—the slight but definite lengthening in conduction, which according to Cohn (11), may occur as early as forty-eight hours after administration of the drug. B. *Changes in the T wave*: (1) diminution in length of wave; (2) inversion of the *T* wave; (3) in cases yielding downwardly directed *T* waves before treatment, digitalis produced eventually upwardly directed waves.

A. *Effect on conduction.* Digitalis may produce depression of conduction in two ways:

(*a*) By direct action on the conducting tissues.

(*b*) By action on the inhibitory system.

In auricular fibrillation it is believed that both these factors play a part, but that in the early stages of administration the effect on the inhibitory system is the more important. The longer the administration is continued the more powerfully does the direct action of the conducting system come into play, until its effect becomes the more important of the two (12).

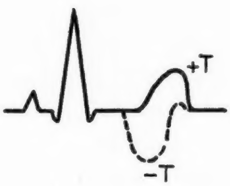
This effect of digitalis is quite different, therefore, from that of strophanthin, which acts entirely on the conducting system and is, therefore, unaffected by atropine.

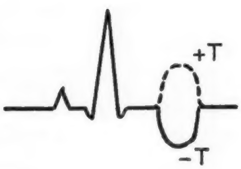
According to Eggleston (13) and Cushny (14) the slowing in cases of normal rhythm is entirely due to inhibitory action.

B. *Changes in the T wave.* Cohn, Fraser, and Jamieson (15) found that alteration in the *T* wave occurred in thirty or thirty-four patients to whom full doses of digitalis were given, and that this alteration was generally observed before alteration in rhythm or conduction time had occurred, or before the onset of gastro-intestinal symptoms.

This effect was found by Eggleston (16) and Wyckoff to occur as early as two to four hours after oral administration.

Cohn (17) has made the observation that in addition to the inversion of the *T* wave it undergoes a change in position, and is considerably nearer the *Q. R. S.* deflexion than the normal upright *T* wave, or the *T* wave which is inverted as the result of myocardial degeneration.





The alterations in the *T* wave have been found to persist for some days after the drug has been discontinued.

Diuresis. Where oedema is present, either apparent or masked, it is usual for a definite diuresis to occur under the influence of digitalis; if, however, oedema be absent, most observers find no diuretic effect, and assume that the fall in urinary output towards the end of treatment is accounted for by the anorexia and nausea with diminished intake of fluid as the toxic symptoms increase (18, 19, 20, 21).

Effects on blood-pressure. According to Eggleston (22) there is no evidence that digitalis has any direct action on the blood-vessels when given to man, even in large therapeutic doses. Changes in the blood-pressure do occur under the influence of digitalis as a result of variations in other factors.

Cohn (23) noticed a fall in pressure in two types of cases: (1) *No oedema, high blood-pressure.* A fall of 30 mm. Hg may occur early in the course of treatment with a tendency towards a return to the former level whether or not the treatment continues. (2) *High blood-pressure with oedema.* A fall generally occurs with the disappearance of the oedema, the level usually remaining low if the patient is not suffering from chronic vascular hypertension.

This observation tends to support the conclusions of Rowntree (24) from his experiments on dogs, that excessive intake of fluid alone will, in dogs, produce all the symptoms of uraemia with rise of blood-pressure and intracranial tension.

Cohn (25) observes no alteration in systolic or diastolic curve in patients with a sinus rhythm, no oedema, and moderate or low blood-pressure.

Luten (26) in his series of cases found no uniform effect on blood-pressure, the commonest result being a temporary rise in systolic and sometimes in diastolic pressure.

Pulse-pressure. Some observers (27, 28) have noticed a marked increase in pulse-pressure in certain cases of normal rhythm under the influence of digitalis, this being chiefly due to the lowering of the diastolic pressure; the rise in pulse-pressure may be only temporary.

Coronary arteries. It has been suggested that digitalis may act on the coronary arteries, causing constriction of the vessels, and is therefore contra-indicated in angina pectoris.

Eggleston (28) believes there is no evidence for this theory, and quotes the work of Meyer and of Sakai and Sancyoski, who have shown that the coronaries do not contract under the influence of digitalis, but if affected at all they probably dilate.

Vital capacity. West and Pratt (29) regard the estimation of vital capacity as a test of considerable value in judging the effects of digitalis, especially in those patients with regular rhythm whose heart-rate changes are slight. Increases of as much as 15 to 20 per cent. have been seen in the first twenty-four hours after the physiological dose, while the records during the preliminary rest period may show but little alteration. They regard as a sign of grave prognosis a vital capacity which, low before treatment, fails to rise during treatment.

Robinson (30) considers this test holds promise as a means of estimating quantitively the functional efficiency of the circulation, and that it should be included in all comprehensive studies of the effects of digitalis in man.

Type of case affected. Assuming that alteration in the heart-rate is not the only criterion of value in estimating the effects of digitalis, but that such facts as the relief of dyspnoea, increase in vital capacity, &c., should be taken into consideration, many cases of dramatic improvement have been recorded. Luten (31), who made a careful study of a series of cases of cardiac failure with normal rhythm, found that 'patients with myocardial insufficiency (characterized by dyspnoea on exertion, enlarged dilated heart, enlarged liver, and oedema) improve under proper digitalis administration in about the same proportion of cases as do patients with auricular fibrillation. The improvement in the former class of cases is usually, perhaps, of somewhat less extent, but it is frequently as impressive as the most striking results that occur in patients with fibrillation of the auricles.'

A similar response in such cases has been noted also by Leech (32), Fraser (33), and Cushny (34). Although not contra-indicated, digitalis appears to be less effective in cases of aortic incompetence than in cases of mitral disease (34, 35).

There is no evidence that digitalis is contra-indicated in cases of high blood-pressure, although it is unusual for much improvement to occur unless oedema is present. This fact was observed by Withering (36), who remarks that 'it seldom succeeds in men of great natural strength, of tense fibre, of warm skin, of florid complexion, or in those with a tight and cordy pulse'.

Digitalis in pneumonia and other fevers. There has been much speculation for many years as to the possible value of digitalis in febrile conditions. Shortly after its introduction by Withering in 1785, the drug enjoyed considerable

popularity as a cure for phthisis and other fevers, although Withering himself was hardly convinced of its usefulness in these cases.

Hamilton, in a careful treatise on digitalis twenty years later, remarks: 'In regard to general fever, while the cause producing this disorder continues to act, I apprehend little effect will be obtained in retarding the velocity of the pulse by the use of digitalis, and that even were this effect constantly and certainly to be depended upon it is doubtful whether this alone would suspend the febrile action or diminish the violence of the other symptoms.'

Mackenzie (37) observes that digitalis has little effect upon the heart-rate when it is accelerated by agents which increase the excitability, as in fever.

Cushny also, as quoted by Robinson, has found digitalis apt to be inefficient when fever is present.

Cohn (38) has observed that in pneumonia digitalis does not alter the sinus rate of the heart, but has the same influence on the T wave and the *a.-v.* interval as in the non-febrile heart. It reduces the ventricular rate when the auricles are in a state of fibrillation or flutter. He considers the frequency with which fibrillation or flutter is liable to occur in pneumonia (9·7 per cent.) an indication for the routine administration of digitalis in pneumonia.

Observations on the size of the heart in pneumonia have been made by Levy (39), who, in a short series of cases, found that dilatation of the heart was less frequent in those patients to whom digitalis was given than in those who did not receive it.

There being, therefore, in the case of failure with normal rhythm no such definite rules for the use of digitalis as in failure with auricular fibrillation, this investigation was undertaken with the object, if possible, of adding something to the knowledge of:

(*a*) The influence, if any, of digitalis in different forms of cardiac failure with normal rhythm;

(*b*) The type of case most affected either as to change in heart-rate or relief of symptoms.

Material and Method of Investigation.

We were faced at the outset with the difficulty of acquiring a sufficient number of cases for a comparative series, the number of patients arriving at a condition of failure with the heart in a state of normal rhythm being relatively rare.

Some few patients were admitted to the wards in too grave a condition to allow of the period of rest without treatment which was regarded as necessary for this investigation, and they could not therefore be included in the series, which consists of nine cases.

In order to obviate as far as possible any error due to the influence of rest only, each patient was standardized by a period of rest in bed without treatment of not less than ten days, and until the heart-rate, urinary output, and body-

weight became stationary. From the time of admission records were kept of: heart-rate (four-hourly); respiration rate (four-hourly); output of urine (daily); weight; and vital capacity; the above factors being charted graphically.

The patient's physical condition on admission was noted and any changes in symptoms or physical signs observed. The Wassermann reaction and non-protein nitrogen (N. P. N.) test were performed in each case and electrocardiographic (E. C. G.) records were taken.

For the vital capacity test a simple water spirometer was used, graduated in cubic centimetres and balanced so that no effort was required to raise the cylinder. The highest of three readings was taken as the vital capacity. This was expressed in percentages of the standard vital capacity of that particular patient, as calculated by West's (40) formula, where the standard vital capacity is determined by multiplying the standing height in centimetres by twenty-five in men and twenty in women.

In patients who were confined to bed the reading was always taken in the sitting position, so that it was not necessary to correct the reading for the diminution which occurs when the reading is taken in the recumbent position—as is shown by the work of Christie and Beams (41) and Rabnovitch (42).

Digitalis dosage. For the purpose of this investigation it was decided to use the B. P. tincture of digitalis. The majority of the patients received one drachm daily, in three doses of twenty minims each, repeated until the onset of nausea and vomiting or other toxic symptoms. The Eggleston (43) method of rapid digitalization, which has proved very successful in cases of auricular fibrillation, where an effect is required at the earliest possible moment, was not considered suitable for the type of case presented in this series.

Results.

Effect on heart-rate. A definite fall in heart-rate was observed with remarkable frequency, occurring in seven of the nine cases. In four there was a decrease of twenty beats per minute or over, in three cases of ten beats per minute. In all the cases except one the fall in heart-rate began from the fourth or fifth day, this being several days before the appearance of subjective toxic symptoms. In two of the cases the heart-rate continued to fall for ten days after the administration of digitalis ceased.

Relation to oedema. Only two of these patients had definite oedema; one other probably had some marked oedema, as there was puffiness of the legs on admission and a loss of weight occurred during the observation period. The weight had, however, begun to rise before the administration of digitalis.

Blood-pressure. No alteration in blood-pressure, either systolic or diastolic, was observed in the two cases of hypertension.

In one patient with considerable oedema there was a fall of 15 mm. Hg in systolic and diastolic pressures when the oedema had disappeared under digitalis.

With the return of oedema after the influence of the digitalis had passed off, a rise in blood-pressure occurred.

In two cases there was a rise in pulse-pressure due to a lowering of diastolic pressure.

Electrocardiograms. In the majority of cases the usual changes due to the influence of digitalis were well marked: (1) slight increase in the pulse-rate interval; (2) inversion of the *T* wave generally in lead III, sometimes also in leads I and II. The characteristic alteration in the shape of the inverted *T* wave described by Cohn (44) was well shown in some cases (see Plate 7).

Diuresis. No very marked diuretic effects were observed in these patients. In the three cases where oedema was present a moderate diuresis occurred on the fourth and fifth days only, simultaneously with the fall in weight. In one case the body-weight continued to fall for three days after the urinary output became low.

A far more constant effect was found to be a later diminution in the amount of urinary secretion. This was found to occur in six of the nine cases, and was noticed two days before the end of treatment in two cases, three days before in two cases, four days before in one case, and seven days before in one case.

As the administration of digitalis ceased in each case with the onset of subjective symptoms of intoxication (nausea, vomiting, or undue palpitation), the diminished urinary output cannot be due to the smaller intake of fluid consequent on the nausea—as is assumed by Cohn (45)—but must be regarded as a definite effect of the drug, and is therefore an early and valuable sign of digitalis toxaemia.

This point confirms the observations of Fraser (46) that 'a reduction in the output of urine is a valuable sign of toxaemia that is often overlooked'.

In some cases the urinary output continued low for several days after the cessation of digitalis.

Digitalis dosage. The majority of the patients were able to tolerate about eight drachms before the onset of toxic symptoms. Four of them, however, continued taking the drug for several days longer without complaining of nausea. It is significant, however, that in each of these cases the fall in urine occurred after about eight drachms had been taken, and that this point should probably have been regarded as the onset of toxaemia.

This being so, the amount of the drug required for full digitalization is remarkably constant for patients with different types and different degrees of failure.

These findings are in accordance with the opinion of Eggleston (47) that there is 'no relation between the dose required for any given effect and the cardiac condition of the patient'. Mackenzie (48) also found that digitalization occurred in a series of patients including those with normal rhythm and auricular fibrillation after the same or approximately the same total dose, which he found to be from five to eight drachms when taken in doses of about one drachm per diem.

Type of Case affected.

Classification.

1. With valvular disease.	*a.* Mitral stenosis	1. With oedema	1
		2. Without oedema . . .	2
	b. Mitral and aortic disease	1. With oedema	1
		2. Without oedema . . .	3
	c. Aortic stenosis	1. With oedema	1
		2. Without oedema . . .	0
2. No valvular disease.	Hypertension		1

Of the patients in this short series there is no doubt that the greatest benefit was derived from the digitalis treatment by those cases of valvular disease which showed marked oedema. Although the effect is not so rapid as in auricular fibrillation it is no less dramatic, the fall in heart-rate and body-weight with diuresis generally occurring about the fourth day.

That a marked fall in heart-rate may occur without any other subjective or objective improvement is shown by two cases—both youths—who may perhaps belong to the class described by Cohn (49) as 'hypodynamic hearts'.

There is no indication from this investigation that one type of valvular disease is more susceptible than another to digitalis therapy. All types respond equally well if congestive failure be present.

Varying degrees of subjective improvement were experienced by other patients. One, with cardiac asthma, had no attacks during the course of digitalis, although they were frequent before and afterwards. One, with considerable dyspnoea and insomnia, found his breathing easier and sleep longer.

Vital capacity was increased during the treatment in six cases. Four patients, in spite of a fall in heart-rate, derived no obvious subjective improvement from the exhibition of digitalis.

Summary.

1. That digitalis is indicated in cardiac failure with normal rhythm when oedema is present, irrespective of the valves affected.

2. That no other definite indication for the use of the drug has been provided by this series, although clinical improvement was noted as a result of its use in certain cases without oedema.

3. That slowing of the heart-rate frequently occurs before the onset of toxic symptoms, but, except in the case of congestive failure, slowing does not necessarily imply subjective improvement.

4. That no diuresis occurs unless oedema be present.

5. That a diminution in the output of urine usually occurs before the onset of gastric symptoms, and should be regarded as an early sign of digitalis intoxication.

Case Reports.

Case I. W. M. M., aged 16. Case of mitral stenosis and aortic regurgitation. ? Adherent pericardium. *Symptoms*: Shortness of breath on exertion and exhaustion on effort for one and a half years. *Aetiology*: No history of rheumatic fever; chorea twice; frequent tonsillitis; pneumonia sixteen months ago, from which he dated the dyspnoea on exertion. *Clinical condition on admission*: A thin, pale youth, considerably under-sized. Slight cyanosis. No clubbing of fingers. No oedema. No enlargement of liver or spleen. No orthopnoea. No cough or expectoration. Urine sp. gr. 1,026. No albumin, casts, or sugar. Teeth and gums healthy. Tonsils enlarged. Non-protein nitrogen 34 mg. per cent. Chest expansion poor—1 in. Vital capacity 1,650 c.c. = 42 per cent. of standard vital capacity. *Heart*. Considerably enlarged, chiefly to the right side—as shown by X-ray. Apex 5 in. from mid-line in sixth space. Systolic thrill over apex. Systolic retraction in fourth and fifth spaces. Systolic and faint diastolic murmurs at the mitral area; faint diastolic murmur down the sternum. Electrocardiogram: broad *P*. *P-R* time increased. Normal rhythm. Blood-pressure 98/70 mm. Hg. Heart-rate 100.

Observations. Before digitalis. Patient rested in bed for fifteen days without treatment. During this time there was slight general improvement, as shown by a fall in heart-rate from 116 to 100, which however rose to 108 the day before digitalis was given.

On digitalis. ʒj of the tincture was given daily for fifteen days. For the first four days the patient had some discomfort—nausea and restlessness. This was accompanied by a rise in heart and respiratory rates. The discomfort had passed off by the fifth day and the heart-rate began to fall steadily from 108 to 72 until the onset of toxic symptoms, after which the digitalis was discontinued. There was a slight diuresis on the third day, followed by a decrease in urinary secretion on the eleventh day, which persisted four days after the digitalis was stopped. There was a slight loss in weight during this period. Vital capacity rose by 8 per cent.

After stopping digitalis. The toxic symptoms passed off in two days, and the patient was allowed up; but as the heart-rate increased he was put back to bed again. He then, unfortunately, had a sharp attack of tonsillitis which lasted for six days and to which the further rise in heart-rate was due. When this was over the heart-rate became stabilized at a rate slightly lower than that existing before the administration of digitalis. A moderate diuresis occurred on the fifth and sixth days after digitalis was stopped. Vital capacity had fallen slightly at the end of this period.

Summary.

The chief feature in this case was the very marked fall in the heart-rate under the administration of digitalis, and the rapid return to the previous level when the influence of digitalis had passed off. There was no appreciable change in any other factor or subjectively (see Chart III).

Case II. J. S. M., aged 44. Case of mitral stenosis and aortic regurgitation. This patient was under observation continuously for a period of four months, during which time the heart passed from a state of normal rhythm into auricular fibrillation. A course of digitalis was given during the period of normal rhythm and again after the onset of fibrillation. *Symptoms*: Dyspnoea, orthopnoea; praecordial pain; cough; insomnia; frequent attacks of 'cardiac asthma'. *Aetiology*: Rheumatic fever twice (at 18 and 34 years), in bed six months each

time. Pneumonia at 25 years. Pleurisy three times. Took alcohol to excess up to two and a half years ago (a bottle of whisky a day). Six months previously patient had a transient attack of loss of power in left arm and leg with aphasia. For six months he had had attacks of 'asthma' (dyspnoea, pallor, profuse sweating, and palpitation), occurring most frequently at night. *Clinical condition on admission*: Spare in build. No cyanosis. No oedema. Had difficulty in breathing even when at rest; the whole chest moved vertically. No engorgement of veins. No enlargement of liver or spleen. Persistent cough. Moist sounds in both lungs. Chest expansion $1\frac{1}{2}$ in. Vital capacity 1,600 or 37 per cent. of standard vital capacity. Non-protein nitrogen 37 mg. per cent. Urine sp. gr. 1,016. No albumin or casts. Wassermann reaction weakly positive. *Heart.* Moderately enlarged. Apex 5 in. to left in fifth space. Diastolic thrill at mitral area. First sound loud and slapping at mitral area. Diastolic and systolic murmurs at mitral area. Soft blowing diastolic murmur at aortic area. Electrocardiogram: normal rhythm. Blood-pressure 125/80. Heart-rate 84.

Observations. Before digitalis. Rest in bed for five weeks without treatment. Very little change occurred in the general condition during this period, the most distressing feature being the frequent severe attacks of 'cardiac asthma'. The attacks occurred most frequently in the early morning, sometimes as a result of the excitement of a 'ward round', sometimes after a change in diet. The attacks began with a feeling of heat and acute dyspnoea, followed by pallor, cyanosis, profuse sweating, and oedema of the lungs with frothy expectoration. The heart-rate during the attacks frequently reached 160 or 170 per minute. The attacks, which lasted from half an hour to two hours, were somewhat relieved by adrenalin or amyl nitrite.

On digitalis. ʒj of the tincture was given daily for nine days and discontinued with the onset of toxic symptoms (nausea and palpitation). During this period patient had no attack of asthma and was able to sleep better and eat better. No change in heart-rate except for the absence of periods of rapid action during the attacks of dyspnoea. Frequent ectopic beats. Slight diuresis third and fifth days. Slight fall in respiratory rate. No change in weight. No change in vital capacity.

After stopping digitalis. Patient remained fairly well and free from attacks for about ten days, after which they recurred with increasing frequency and severity for about five weeks.

Onset of fibrillation. Auricular fibrillation occurred after one of the attacks of 'asthma'. With the onset patient felt very ill. Ventricular rate very rapid (160), irregular. Some respiratory distress, though very much less than during the periods of rapid action associated with the asthma. A moderate degree of oedema of legs and hands ensued in the next few days. Electrocardiogram proved the change to auricular fibrillation.

Digitalis with auricular fibrillation. Tr. digitalis ʒss. given daily. Rapid fall in heart-rate from the second day (from 160 to 84 in eight days). Rapid fall in respiratory rate (from 30 to 20 in eight days). Marked diuresis from the fourth day. Marked decrease in vital capacity—17 per cent. No appreciable change in blood-pressure.

Subjectively. The condition of the patient much improved. The attacks of asthma did not recur. Patient slept better and the appetite became good. Oedema disappeared.

Summary.

Comparison of the action of digitalis with (a) *Normal rhythm.* No change in heart-rate. Slight fall in respiratory rate. Diuresis fourth to ninth days, followed by fall. (b) *Auricular fibrillation.* Rapid fall in heart-rate (from 160 to 84 in

eight days). Marked fall in respiratory rate (31 to 20 in eight days). Marked diuresis fourth and fifth days (see Chart IV).

It is interesting that although there was less repiratory distress after the establishment of fibrillation the vital capacity decreased by 17 per cent.

Case III. M. W. M., aged 56. Case of aortic stenosis with a moderate degree of regurgitation. *Symptoms*: Dyspnoea for twelve months; cough, oedema, and insomnia for nine months. *Aetiology*: No history of rheumatism, chorea, or infective fevers. Patient had been able to work up to twelve months ago. For four months previous to admission he had been in bed at home. The medicinal treatment given in this period could not be ascertained.

Clinical condition on admission: Patient showed evidence of recent loss of weight. Considerable oedema of the legs and back. Marked ascites. Liver palpable at the level of the umbilicus. Tenderness of abdominal wall in the right upper quadrant. Cough, with frothy, rusty expectoration. Moist sounds present at both bases. No free fluid in chest. Urine sp. gr. 1,020. Trace of albumin. No casts. Non-protein nitrogen 33 mg. per cent. Wassermann reaction negative. Vital capacity 600 c.c. 17 per cent. of standard vital capacity. *Heart.* Considerably enlarged; apex beat diffuse; 7 in. from mid-line in sixth space. Systolic thrill at aortic area. Sounds soft at all areas. Faint diastolic murmur at the lower end of sternum. Pulse not markedly collapsing. Heart-rate 86, regular. Arteries not thickened. Blood-pressure 135/95 mm. Hg. Electrocardiogram: normal rhythm. Inverted *T* in leads I and II. Left ventricular preponderance.

Observations. Before digitalis. Rest in bed for fourteen days without treatment resulted in some general improvement as shown by: (1) decrease in amount of oedema, associated with (2) moderate diuresis tenth to twelfth days; (3) loss of 4 lb. in weight.

On digitalis. Tr. digitalis ʒj was given daily for eight days. There was considerable general improvement, the chief feature being a rapid loss of weight—14 lb. in eight days. Diuresis occurred on the second to fifth days, followed by a fall in the amount of urine on the sixth to eighth days. Heart-rate was reduced from 88 to 80. Vital capacity increased by 5 per cent. Nausea and vomiting occurred on the eighth day and digitalis was stopped.

After digitalis was stopped. Improvement was maintained for a few days only. The heart-rate continued to fall for ten days (80 to 86). Weight began to rise after the third day (15 lb. in thirteen days). Ascites and oedema increased.

Summary.

A definite response to digitalis was shown in this case, the chief features of which were the rapid loss of weight and decrease in oedema coincident with a marked diuresis, followed by a rapid increase in weight and oedema on its cessation—in spite of the fact that the heart-rate continued to fall for five days after the body-weight had begun to rise. The urinary output, which had diminished three days before the cessation of digitalis, remained low.

Case IV. E. W. F., aged 26. Case of mitral regurgitation with some stenosis. This patient was under observation for two periods separated by a two months' interval. The first period was characterized by a moderate degree of cardiac failure, as shown by dyspnoea, slight oedema, and a rapid heart action with normal rhythm. After five weeks' rest and treatment the patient was able to return home, where she remained able to take light exercise until a fortnight

before admission for the second time. On readmission the degree of cardiac failure was profound and characterized by massive oedema, nausea, vomiting, jaundice, and a rapid heart-rate, shown by the electrocardiogram to be due to auricular flutter. The patient's condition at this time was very grave, and a fatal issue seemed imminent. An attempt was made to change the flutter into fibrillation by the administration of digitalis. Tr. digitalis ʒj ss. was given daily for three days, but was not retained owing to the persistent vomiting. Strophanthin intravenously had no obvious effect. On the eighth day Nativelle's granules ($\frac{1}{240}$ gr.), six per diem ($= \frac{1}{40}$ gr. digitalin), were given and retained, and three days later the flutter passed into fibrillation, from which time the patient began to improve. We were thus able to compare the action of digitalis in the same patient with the heart: (1) in a state of normal rhythm, (2) in auricular fibrillation.

First period. Symptoms: Dyspnoea, about two years; orthopnoea, six weeks. *Aetiology*: No history of rheumatic fever or chorea; frequent tonsillitis. About three months before admission patient had painful and swollen joints (knees, ankles, elbows, and wrists), but did not go to bed. *Clinical condition on admission*: Slight in build, pale, with a malar flush. Some oedema of the legs. Liver slightly enlarged. No tenderness of the abdominal wall. Cough troublesome at night; numerous crackles in the lower half of each lung. Tonsils not enlarged, but showed scars. Urine sp. gr. 1,020. No albumin or casts. Non-protein nitrogen 26 mg. per cent. Wassermann reaction completely negative. Vital capacity 1,000 c.c. = 33 per cent. of standard vital capacity. *Heart.* Slightly enlarged. Apex $4\frac{1}{4}$ in. to left in fifth space. Substernal heaving. Presystolic thrill. Systolic murmur at the apex conducted to the axilla; diastolic murmur to the right of the apex, with presystolic accentuation. Pulse not collapsing. Arteries not thickened. Blood-pressure 120/75 mm. Hg. Heart-rate 112 regular. Electrocardiogram: *P* broad. Normal rhythm.

Observations. Before digitalis. Patient rested in bed for eleven days with considerable general improvement. Heart-rate decreased (120 to 108). Loss of 7 lb. in weight in ten days. Increase in vital capacity 10 per cent. Slight diuresis on the fifth day with disappearance of the oedema. Patient felt better, slept better, and had less palpitation.

On digitalis. Tr. digitalis ʒj daily given for nine days. Rapid fall in heart-rate (108–82). Loss of weight—2 lb. Diuresis fourth and fifth days. Rise in vital capacity 15 per cent. Some subjective improvement; patient had better nights and less palpitation.

After stopping digitalis. Heart-rate continued to fall for a few days, but rose again to 100 when patient began to get up. Palpitation still present (see Chart I).

Summary.

Considerable improvement occurred with rest in bed only, as shown by the fall in heart-rate, increase in vital capacity, and considerable loss in weight, which latter had begun to increase before digitalis was given. Definite response to digitalis. Marked fall in the heart-rate, which began on the fourth day coincident with a diuresis. Further loss of weight—2 lb., with the diuresis, followed by a slight rise.

Second period. Symptoms: Considerable dyspnoea; swelling of arms, face, legs, and abdomen; nausea and vomiting.

Clinical condition on admission: General massive oedema. Liver enlarged, reached $\frac{1}{2}$ in. below umbilicus. Tenderness of abdominal wall on palpation. Persistent vomiting. Slight jaundice. Both lungs congested. No free fluid.

Heart. Considerably dilated. Apex-beat slapping, 6 in. to left in eighth space. Heart-sounds soft. Diastolic murmur down the sternum, with no presystolic accentuation. Engorgement of veins in the neck. Ventricular rate 128, regular. Electrocardiogram: auricular flutter, 2 : 1.

The condition being one of urgency, tincture of digitalis was given daily, ʒj ss. in twenty-four hours, but was not retained owing to the vomiting, which became more persistent. The patient's condition became worse; the jaundice increased, the ventricular rate more rapid (144), oedema greater. Restlessness and distress were more marked. On the sixth day strophanthin, 0·5 mg., was given intravenously without obvious effect. Two days later Nativelle's granules ($\frac{1}{40}$ gr. digitalin per diem) were given and retained. Slight improvement in condition followed, as shown by a desire for food. On the tenth day there was a period of 4 : 1 rhythm, ventricular rate 76. On the morning of the eleventh day the heart passed into auricular fibrillation, the patient being conscious of the change in rhythm. With the onset of fibrillation there was a marked fall in the ventricular rate to below 80, also in the respiratory rate, the patient being already fully digitalized. Contrary to expectation the daily excretion of urine diminished and the oedema and jaundice increased. After ten days, the excretion of urine being still low, fluid began to collect in the right pleural cavity. Three pints of fluid were aspirated, and this operation had to be repeated thrice—a total of twelve pints being removed in twenty days, after which a diuresis occurred, and coincident with this the fluid disappeared from the pleural cavity and did not again accumulate. The patient then made a slow but uninterrupted recovery (see Chart I).

Summary.

Three periods to be considered: (1) the heart in normal rhythm; (2) the heart in auricular flutter; (3) the heart in auricular fibrillation.

1. *Normal rhythm.* Definite response to digitalis as shown by: (*a*) marked fall in heart-rate, continued after disappearance of all oedema and after body-weight had begun to rise; (*b*) increase in vital capacity; (*c*) diuresis.

2. *Auricular flutter.* Very little digitalis retained for first six days owing to vomiting. Patient's condition grew rapidly worse. No fall in ventricular rate. Flutter changed from 2 : 1 to 4 : 1 and then into fibrillation.

3. *Auricular fibrillation.* Patient already digitalized fully. Rapid fall in ventricular rate. No diuresis, but definite anuria associated with increase in oedema and jaundice, and later pleural effusion. After five weeks a diuresis occurred and the oedema and pleural fluid disappeared.

The action of digitalis in this case, allowing for the difference in the patient's condition, was quite as dramatic in the heart in normal rhythm as in a state of auricular fibrillation.

Case V. Mrs. A. D., aged 43. Case of mitral stenosis and renal disease. *Symptoms*: Dyspnoea on exertion for two years. Pain under the heart for six months. Dyspnoea without exertion, and oedema for six weeks. *Aetiology*: Rheumatic fever three times, the last ten years ago; chorea twice; tonsillitis twice; typhoid fever, scarlet fever, influenza two years ago. The dyspnoea on exertion followed the influenza two years ago, since when there had been frequent cough with occasionally blood-stained sputum. The dyspnoea became much worse with the onset of oedema. There had been aching pain under the heart, not particularly associated with exertion, for six months. *Condition on*

admission: Of stout build. Lips slightly cyanosed; malar flush. Moderate degree of oedema of both legs, particularly left. Liver and spleen both palpable. Cough, mostly in mornings. Occasional crepitations at both bases. Non-protein nitrogen 33 mg. per cent. Wassermann reaction negative. Vital capacity 1,050 = 33 per cent. of standard vital capacity. Urine albumin + +; occasional granular and hyaline casts. Weight 11 st. 3 lb. *Heart.* Apex-beat diffuse in fifth space 5 in. from mid-line. Deep cardiac dullness 2 in. to right of sternum. Presystolic and faint systolic mitral murmurs. Electrocardiogram: low voltage; normal rhythm. Blood-pressure 160/90 mm. Hg. Heart-rate 104. Arteries not palpable.

Observations. Before digitalis. Patient rested in bed for fourteen days without treatment. For the first few days there was slight improvement in the general condition. There was a loss of 3 lb. in weight with some diminution in the amount of oedema. After ten days, however, the weight and oedema increased, there was more albumin in the urine, and a cough with blood-stained sputum. The heart-rate also rose—86–96.

On digitalis. For three days ♏xc of the tincture were given daily, but the patient complained of palpitation. ♏lx were given on the next two days, but were reduced to ♏xxx as the palpitation persisted and the nausea increased. This dose was then given for seven days with no discomfort. A rapid fall in weight occurred, the patient losing 11 lb. in eleven days with disappearance of the oedema. The fall in weight was coincident with a sharp diuresis which occurred on the fourth and fifth days. There was also a slight but steady fall in the heart-rate from the second to eleventh days. A rise of 11 per cent. in vital capacity. Albumin disappeared from the urine.

After digitalis. The condition remained about the same for three weeks, after which the oedema began to return and the weight to increase. Albumin reappeared in the urine. Novasurol, 1 grm., was given and resulted in a moderate diuresis within twenty-four hours and a loss in weight of 6 lb. in the four subsequent days. Novasurol was repeated in seven days' time, causing a definite diuresis but a loss of only 1 lb. in weight. A week later the patient was given tr. digitalis ♏xxx and urea grm. xv daily for eighteen days, with the following results: (1) steady fall in heart-rate (96–80); (2) increased daily secretion of urine; (3) steady loss in weight—11 lb. in eighteen days; (4) oedema almost disappeared; (5) patient felt very much better and was able to go home.

Summary.

There was a definite response to digitalis in this case, most marked in the rapid loss in weight and decrease in oedema—beginning with the diuresis which occurred on the fourth day and continuing for three days after the urine fell below normal. The fall in heart-rate occurred from the second day. Smaller doses of tr. digitalis (ʒ ss. daily) given together with urea grm. xv caused a steady but more gradual fall in weight and heart-rate, but the diuresis was maintained (see Chart II).

Case VI. J. G. M., aged 69. Case of high blood-pressure and chronic renal disease with rapid action of the heart due to cardiac failure. *Symptoms*: Palpitation. Breathlessness. Liable to sudden attacks of dyspnoea during the night. *Aetiology*: No history of rheumatism, chorea, or scarlet fever. Typhoid fever forty years ago. Healthy up to one year before admission, when he had to give up work because of increasing breathlessness. *Clinical condition on admission*: Appetite good; sleep moderate. Well-marked arcus senilis. No oedema. Orthopnoea. Well-marked Cheyne-Stokes breathing. Emphysema. Occasional

râles at left base. Examination of occular fundi showed 'edges of the disks blurred, especially of the left, and in that eye are numerous patches of exudate typical of albuminuric retinitis'. Vital capacity 1,400 c.c., or 32 per cent. of standard vital capacity. Non-protein nitrogen 53 per cent. *Urea concentration test*: Before urea 180 c.c. and 2·6 grm. per cent. of urea. Spec. A, 34 c.c. and 2·8 grm. per cent. of urea; spec. B, 63 c.c. and 2·9 grm. per cent. of urea. Urine contained 8 grm. per litre of albumin. No casts seen. Weight 14 st. 9 lb. *Heart.* Considerably enlarged. Apex 6 in. to left in sixth space. Aortic second loud and ringing. No murmurs. Occasional premature beats. Blood-pressure 230/135 mm. Hg. Heart-rate 100. Arteries thickened and tortuous. Electrocardiogram: left ventricular preponderance. Auricular premature beats. *P* inverted in lead III.

Observations. Before digitalis. Patient rested in bed for ten days. No alteration observed in heart-rate or in weight. Some diuresis on the eighth day. No alteration in Cheyne-Stokes breathing. Had two attacks of sudden dyspnoea during the night, relieved by nepenthe. Albumin decreased from 8 grm. per litre to 2 grm. per litre.

On digitalis. Tr. digitalis ♏xlv given daily for seven days. Slight general improvement during this period. Fall in heart-rate from 100 to 86. Loss of 4 lb. in weight. Moderate diuresis on the fourth day. Slight fall in blood-pressure, 205/145. Heart-rate 100. Albumin decreased to 0·5 grm. per litre.

After stopping digitalis. Condition remained about the same for eight days, after which the heart-rate began to rise. Attacks of dyspnoea still occurred during the night. Cheyne-Stokes breathing rather less marked.

Digitalis. ʒ ss. daily was renewed after nine days and continued for thirty-three days. During this time patient gradually improved, and had quieter nights under the action of nepenthe. The Cheyne-Stokes breathing gradually gave place to normal respiration.

Summary.

Primarily a condition of chronic interstitial nephritis with albuminuric retinitis and some cardiac inadequacy. The evidence of cardiac failure in this man were mainly: (1) Very considerable dyspnoea on effort; (2) an increased heart-rate. The conditions were complicated by the paroxysmal dyspnoea and Cheyne-Stokes breathing due to his renal inadequacy. There was no definite effect traceable to digitalis, the gradual improvement being probably due to prolonged rest in bed and the nightly administration of nepenthe.

Case VII. W. H. G. M., aged 34. Case of mitral and aortic stenosis. *Symptoms:* Pain: (1) dull ache over praecordium; (2) superficial tenderness at apical area (cardiac thrust); (3) frequent attacks of sharp pain behind sternum, lasting a few seconds, radiating down inner side of left arm to elbow. Dyspnoea and orthopnoea, three years' duration; cough, with frothy expectoration; insomnia. *Aetiology*: Rheumatic fever fourteen years ago. Was in bed fourteen weeks for influenza seven years ago, followed by the onset of the praecordial pain and frequent haemoptyses (averaging a cupful a day for one month). Since this time, patient had been able to work as a wood-cutting machinist on and off, generally working about six months and resting one month. Patient had been much worse the last twelve months. *Clinical condition on admission*: No cyanosis. Moderate degree of oedema of legs. No enlargement of liver or spleen. Orthopnoea. Cough very troublesome with frothy expectoration. Moist sounds present at both bases. Emphysema—chest expansion poor, ½ in. Vital capacity 1,800 c.c., or 42 per cent.

of standard vital capacity. Non-protein nitrogen 28 mg. per cent. Wassermann reaction negative. Urine sp. gr. 1,015, acid. No albumin, casts, or sugar. Weight 9 st. 7 lb. *Heart.* Considerably enlarged to right and left (confirmed by X-ray). Apex 6 in. to left in sixth space. Systolic thrill above the right clavicle. Systolic bruit at the apex conducted to the axilla. All sounds practically inaudible. Diastolic murmur at lower end of sternum with a systolic bruit at the upper end. Systolic murmur at apex audible in the axilla. Blood-pressure 158/50 mm. Hg. Heart-rate 80. Electrocardiogram: pulse-rate + *Q. R. S.* bizarre. Inverted *T* in leads I, II, III.

Observations. Before digitalis. Patient rested in bed for twenty-five days without treatment. During this period there was a moderate degree of general improvement. The oedema of the legs disappeared with a slight diuresis which occurred on the fifth day. The cough, though still troublesome, was rather less. Patient had better nights, sleeping about four to five hours at a time. The heart-rate fell in the first five days from 97 to an average of 80 per min. Fall in respirations from 34 to average of 26 per min. No change in weight. Rise in vital capacity of 3 per cent.

On digitalis. ʒj of the tincture was given daily for fifteen days and then stopped, although no toxic symptoms had occurred. There was no nausea or abnormal rhythm. Very little change occurred during the course of digitalis administration. There was a slight fall in heart-rate from 80 to 74. A moderate diuresis occurred on the eleventh day. Rise in vital capacity of 11 per cent. There was no change in weight. Subjectively, patient stated that he felt better; was able to sleep better and eat better. The cough remained troublesome and the frothy expectoration remained about the same in amount.

After stopping digitalis. The patient remained under observation for fifteen days. There was a slight rise in heart-rate—74 to 80, to the level before the administration of digitalis. A rise in weight of 2 lb. The cough remained troublesome.

Summary.

There was very little change in the patient's condition definitely attributable to the digitalis administration; two factors only being influenced: (1) slight but definite fall in heart-rate; (2) rise of 11 per cent. in vital capacity.

Case VIII. J. R. F., aged 27. Case of mitral stenosis and neurasthenia. *Symptoms*: Dyspnoea on exertion for six months; orthopnoea for five weeks; palpitation for six months. *Aetiology*: No history of rheumatic fever, chorea, or tonsillitis. 'Muscular rheumatism' for the last six years. Influenza two years ago. No discomfort until six months ago, when patient began to have dyspnoea on exertion, giddiness on going upstairs, and palpitation worse at nights, associated with nausea and pain over the praecordium. Six months ago patient had a cough with blood-stained sputum. *Condition on admission*: Well nourished, inclined to be stout. Slightly cyanosed cheeks. Orthopnoea. Slight cough. No oedema. No enlargement of liver or spleen. Non-protein nitrogen 30 mg. per cent. Wassermann reaction negative. Urine sp. gr. 1,023. No albumin or casts. Weight 11 st. Teeth good. Tonsils not enlarged. Vital capacity 2,500 c.c., or 77 per cent. of standard vital capacity. *Heart.* Apex 4 in. from middle line in fifth space. Presystolic thrill at the apex. At mitral area, first sound loud. Pulmonary second sound accentuated and reduplicated. Diastolic and presystolic murmurs present at the apex. Electrocardiogram: normal. Blood-pressure 120/80 mg. Hg. Heart-rate 100.

Observations. Before digitalis. Patient rested in bed for fourteen days without treatment. General condition improved. There were no night attacks of palpitation; patient slept well. The heart-rate, variable the first few days, became stabilized at 97 per minute.

On digitalis. ʒj of the tincture was given daily for nine days. During the whole of this period patient complained of epigastric pain, which became worse on the eighth day, and on the ninth day each dose of digitalis was vomited. There was no alteration in the heart rhythm. Excretion of urine was low throughout the period, a slight increase occurring on the sixth day. After four days the heart-rate fell slightly (from 96 to 88) until the onset of toxic symptoms on the eighth day.

After stopping digitalis. The toxic symptoms passed off in twenty-four hours and there was no further epigastric pain. The heart-rate returned to the level reached before digitalis was given. Patient continued to sleep well.

Summary.

There was in this case a large element of neurosis due to overstrain and domestic anxieties. The undoubted improvement which occurred while under observation was probably largely due to rest in bed and change in environment. The only factor which was influenced by digitalis was the heart-rate, which showed a small but definite fall.

Case IX. J. H. M., aged 17. Case of mitral stenosis. *Symptoms*: Breathlessness and cough for two and a half years. *Aetiology*: No history of rheumatic fever; growing pains as a child; frequent sore throats; scarlet fever at six years; diphtheria at seven years. Patient had always been undersized; never wanted to play games, but was fairly well until two and a half years ago, when he became troubled with cough and breathlessness. Was in hospital eighteen months, aged 14½ years, with a certain degree of cardiac failure (dyspnoea, cough, and moderate oedema). Cough remained more or less persistent, but patient was able to do light work for nine months, up to a month before admission. *Clinical condition on admission*: Small undeveloped boy (looked about 14). Lips and cheeks somewhat cyanosed. No clubbing of fingers. Appetite fairly good. Slept badly because of persistent cough. Orthopnoea. Harsh breathing in both lungs. No adventitious sounds. Chest pigeon-shaped. Liver enlarged—felt 1½ in. above umbilicus. Tenderness of abdominal wall in right upper quadrant. Urine sp. gr. 1,012. Albumin present. No casts seen. Weight 4 st. 12 lb. Wassermann reaction negative. Vital capacity 1,100 c.c., or 34 per cent. of standard vital capacity. *Heart.* Enlarged; deep cardiac dullness 1½ in. to right of sternum. Apex 4 in. to left in sixth space. Substernal heaving with systolic retraction in epigastrium. Presystolic thrill at the apex. First sound loud and slapping at mitral area; second sound in pulmonic area. Diastolic and soft systolic murmurs at mitral area.

Observations. Before digitalis. Patient rested in bed for six days without treatment. There was a rapid fall in heart-rate for three days (from 132 to 104), together with a fall in respiration rate and an increase in urinary secretion.

The heart-rate continued to rise from the fourth day to 120. As the patient was in some distress and the condition undoubtedly grave, it was decided not to postpone the digitalis treatment any longer.

On digitalis. Tr. digitalis ♏xl given daily for fourteen days. Rapid fall in heart-rate from fourth to tenth days (122 to 90), followed by a rise from the eleventh day. Secretion of urine remained high for eight days with a moderate diuresis on the sixth day, after which it decreased in amount for three days, coincident with the rise in heart-rate, but rose again on the twelfth day. The patient's condition became increasingly grave, and on the morning of the fifteenth day, after a fair night and breakfast as usual, he died suddenly without any warning.

Analysis showing Effects of Digitalis.

Ada D., aged 43. **Heart lesion**: Mitral stenosis; renal disease; blood-pressure 160/90 mm. Hg; heart-rate 104. **Symptoms**: Rheumatic history; dyspnoea; haemoptysis; praecordial pain; oedema. **Amount of digitalis**: (*a*) ʒxiij in 13 days. (*b*) Digitalis ʒss., urea grm. xv for 18 days. **Heart-rate**: Slight fall (20); steady fall (100–80). **Urine**: Rise 4–5 days; fall 6–13 days; rise. **Vital capacity**: Rise 13 per cent. **Weight**: Loss 12 lb. 4–8 days. **Chief features of case**: Rapid loss of weight and oedema with diuresis; improvement maintained for a month, followed by rise in heart-rate, oedema of legs, diminution of urine, general improvement.

Wm. H. G., aged 34. **Heart lesion**: Mitral and aortic stenosis; ? left bundle lesion: bizarre *Q. R. S.* **Symptoms**: Rheumatic history; dyspnoea; praecordial pain; insomnia. **Amount of digitalis**: ʒxv in 15 days. **Heart-rate**: No change; slow fall 9–14 days, 10 per minute. **Urine**: Slight rise, 12th day; no anuresis. **Vital capacity**: Rise 9 per cent. **Weight**: No change. **Chief features of case**: Slight general improvement; slept better.

J. G., aged 69. **Heart lesion**: No V. D. H.; hypertension; blood-pressure 220/135 mm. Hg; Heart-rate 100. **Symptoms**: Dyspnoea; Cheyne-Stokes breathing; cardiac asthma. **Amount of digitalis**: ʒvj in 7 days. **Heart-rate**: Fall from 3rd day. **Urine**: No change. **Weight**: Gradual loss. **Chief features of case**: No marked effect; general improvement mostly due to rest in bed and nepenthe at night.

Eliza W., aged 26. **Heart lesion**: (*a*) Mitral stenosis and regurgitation; ? aortic regurgitation. (*b*) Heart dilated; $2\frac{1}{4}$ in. increase; auricular flutter followed by fibrillation. **Symptoms**: (*a*) Recent rheumatism; dyspnoea. (*b*) 2 months later: great dyspnoea; massive oedema; jaundice; vomiting. **Amount of digitalis**: (*a*) ʒix in 9 days; (*b*) Tr. digitalis not retained; Nativelle's granules gr. $\frac{1}{240}$, 6 per diem. **Heart-rate**: (*a*) Fall from 5th day. (*b*) Rapid fall after onset of fibrillation (120–60). **Urine**: (*a*) Rise 4th and 5th days. (*b*) No diuresis. **Vital capacity**: (*a*) Rise 14 per cent. (*b*) Much lower in fibrillation. **Weight**: (*a*) Loss 6 lb. in 4 days. **Chief features of case**: (*a*) General improvement; fall in heart-rate; diuresis. (*b*) Rapid failure during period of flutter with gradual recovery after fibrillation; fluid in right chest aspirated four times, followed by diuresis and loss of oedema.

Jessie R., aged 27. **Heart lesion**: Mitral stenosis; neurotic. **Symptoms**: Dyspnoea; palpitation; haemoptysis. **Amount of digitalis**: ʒix in 9 days. **Heart-rate**: Slight fall. **Urine**: No rise. **Vital capacity**: No change. **Weight**: Loss of 3 lb. **Chief features of case**: No definite improvement.

Jn. H., aged 17. **Heart lesion**: Mitral stenosis. **Symptoms**: Dyspnoea; cough. **Amount of digitalis**: ʒx in 15 days. **Heart-rate**: Marked fall after 3 days. **Urine**: No rise; marked fall after 7 days. **Weight**: No change. **Chief features of case**: Rapid fall in heart-rate; no improvement; died suddenly.

Wm. M., aged 16. **Heart lesion**: Mitral stenosis; aortic regurgitation; ? adherent pericardium. **Symptoms**: History of chorea; dyspnoea on exertion. **Amount of digitalis**: ʒxv in 15 days. **Heart-rate**: Marked fall from 4th day. **Urine**: No rise; fall after 8th day. **Vital capacity**: Rise 12 per cent. **Weight**: No change. **Chief features of case**: Definite fall in heart-rate while on digitalis, followed by rise afterwards.

Max W., aged 56. **Heart lesion**: Aortic stenosis with regurgitation. **Symptoms**: Dyspnoea; cough; insomnia; oedema. **Amount of digitalis**: ʒviij in 8 days. **Heart-rate**: Fall after 4th day (90 to 80). **Urine**: Slight rise 3rd day; fall 6th–9th days. **Vital capacity**: Rise 17 per cent. **Weight**: Rapid loss 3rd day; 14 lb. in 8 days. **Chief features of case**: Rapid loss of weight and oedema, followed by rise in weight, and return of oedema after cessation of digitalis.

J. S., aged 44. **Heart lesion**: (*a*) Mitral stenosis; aortic regurgitation. (*b*) Auricular fibrillation. **Symptoms**: (*a*) Rheumatic history; dyspnoea; praecordial pain; cough; insomnia; cardiac asthma. **Amount of digitalis**: (*a*) ʒix in 9 days; (*b*) ʒ ss. daily for 18 days. **Heart-rate**: (*a*) No change; (*b*) Rapid fall (140 to 80). **Urine**: (*a*) Slight rise 3rd–6th days; (*b*) steady rise. **Vital capacity**: (*a*) No change; (*b*) lower with auricular fibrillation. **Weight**: (*a*) No change; (*b*) no change. **Chief features of case**: (*a*) No change; increasing distress with very severe attacks of dyspnoea and rapid heart-rate until the onset of auricular fibrillation. (*b*) Disappearance of 'asthmatic' attacks; rapid fall in heart-rate and rise in urine.

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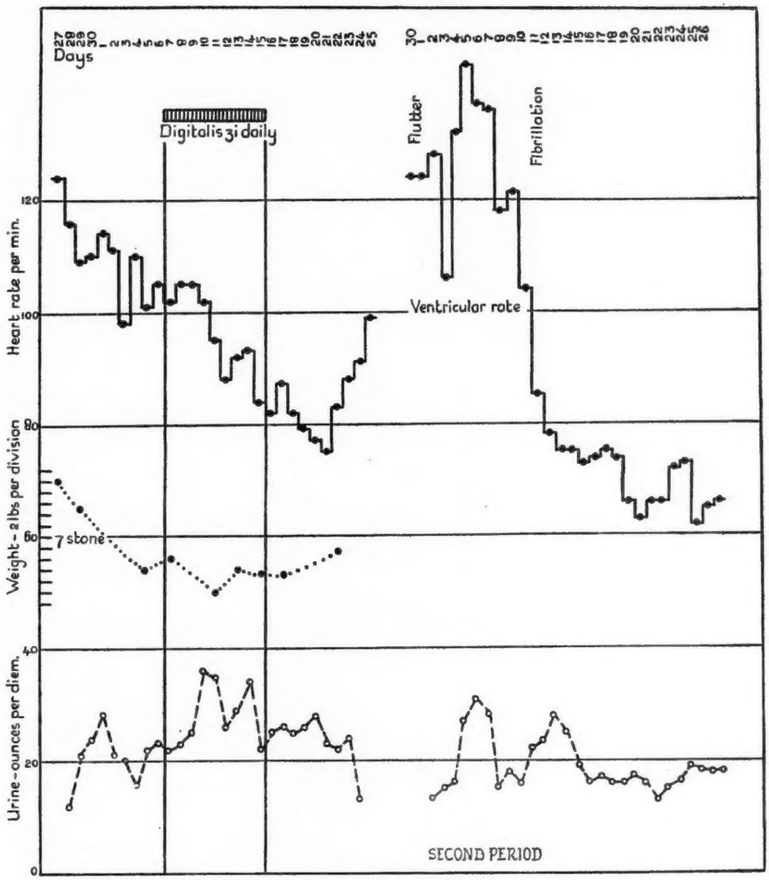

CHART I. CASE IV.

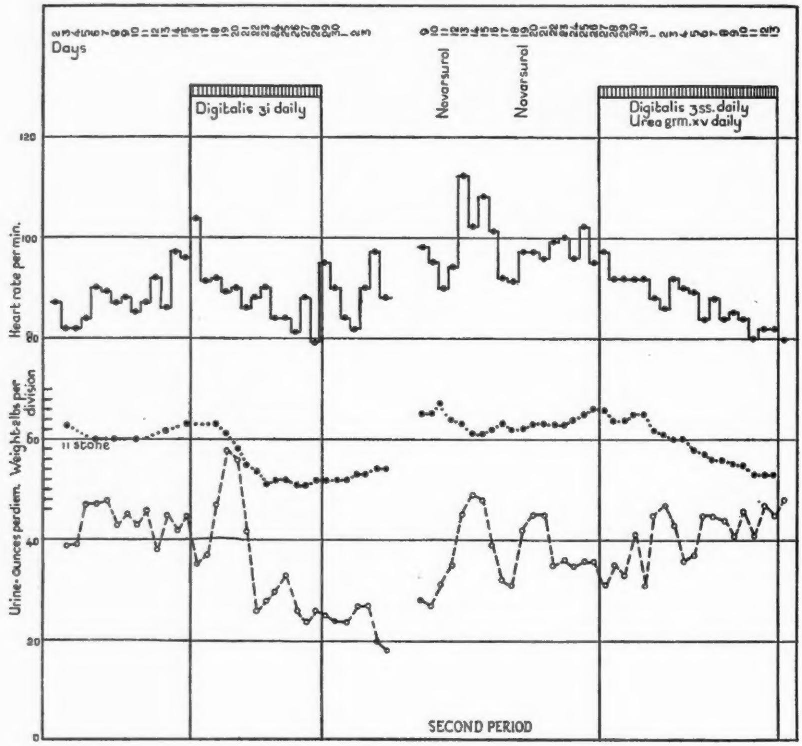

CHART II. CASE V.

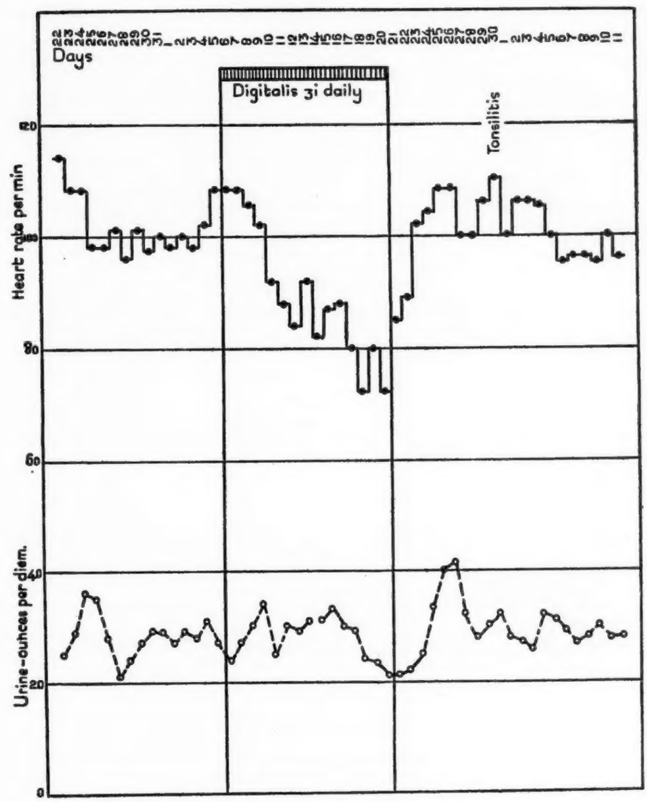

CHART III. CASE I.

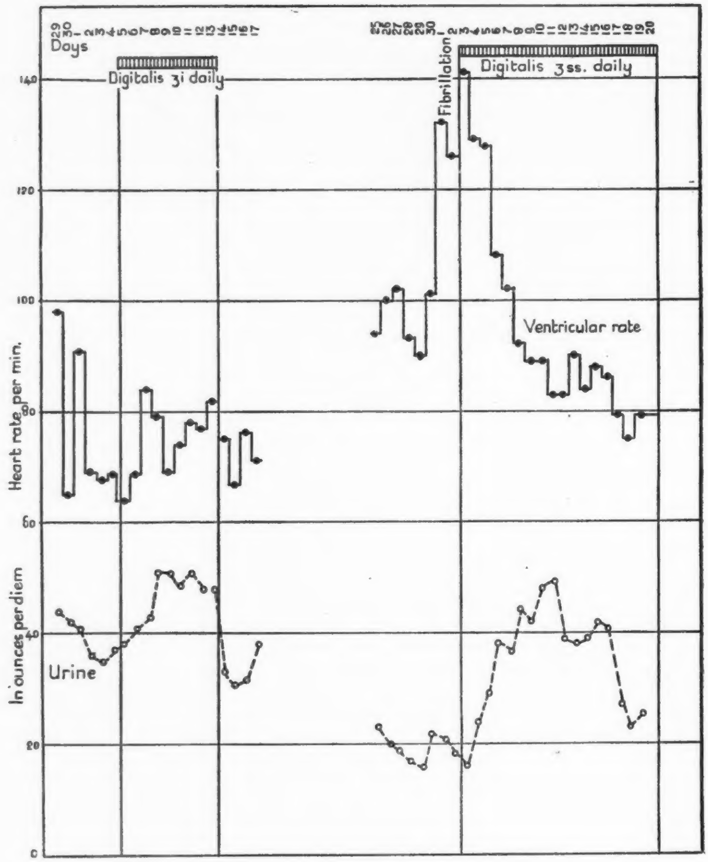

CHART IV. CASE II.

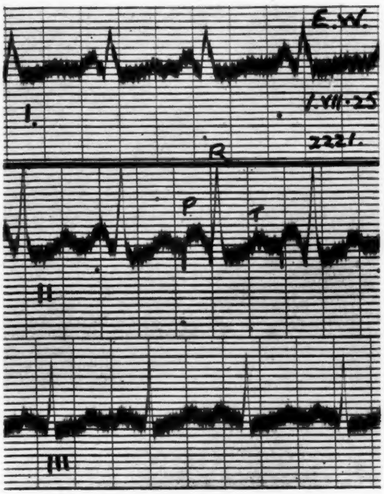

FIG. 1. Five days before the administration of digitalis. Case IV.

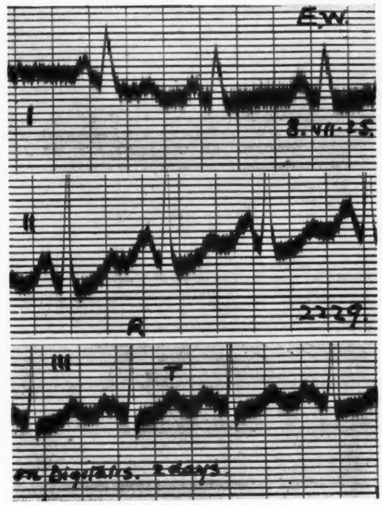

FIG. 2. After two days' digitalization. Case IV.

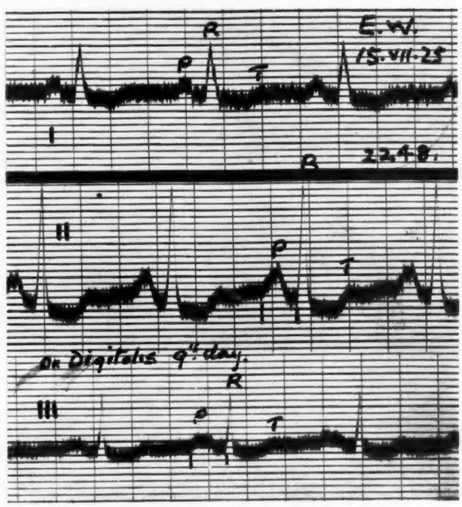

FIG. 3. After nine days' digitalization. Significant change in *T*. Case IV.

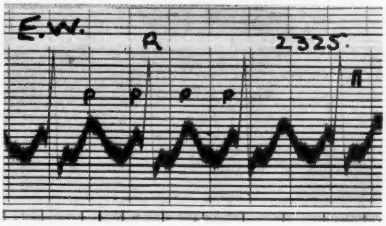

FIG. 4. Auricular flutter, 2:1 rhythm. Case IV

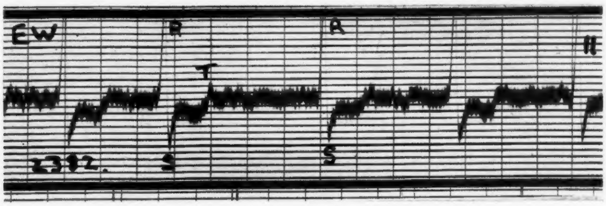

FIG. 5. Auricular fibrillation. Case IV.

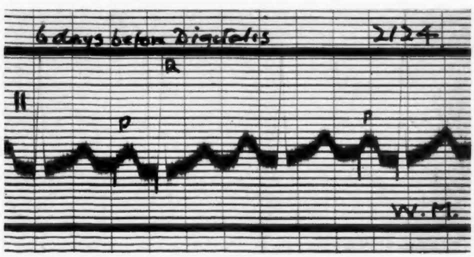

FIG. 6. Six days before administration of digitalis. Normal rhythm. *P–R* interval slightly prolonged. *P* broad. Case III.

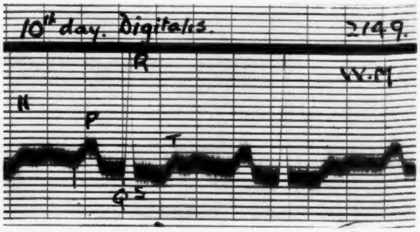

FIG. 7. After ten days' digitalis. *T* inverted in lead II. Prolongation of *P–R* interval more marked. Case III.

THE SEBORRHOEIC FACIES AS A MANIFESTATION OF POST-ENCEPHALITIC PARKINSONISM AND ALLIED DISORDERS[1]

By DAVID KRESTIN
(From the Wards of the London Hospital)

With Plate 9

Introduction.

ATTENTION was drawn to this subject by the frequency with which an unusual greasiness of the skin was observed in patients suffering from the effects of epidemic *encephalitis lethargica*. The appearance of cutaneous lesions during the acute phases of this disease is well recognized. Erythematous, morbilliform, and even petechial rashes occur during the febrile period, but these are transitory and infrequent, and do not differ essentially from similar eruptions of other pyrexial and infective disorders. The presence of a more constant and lasting condition, seborrhoeic in character and apparently independent of pyrexia, does not appear to have attracted much notice, particularly in English-speaking countries. It is described here, not only because of its relative frequency and prominence, but also to emphasize the ever-increasing importance of the association of organic brain disease with disorders attributable to disturbance of the vegetative nervous system, as well as the particular control exercised by this system over cutaneous secretion.

The condition about to be described was first noticed by Cohn (5) in 1920, and soon after by Sarbó (17), both of whom observed it in early or acute cases, and considered it a manifestation of the nervous lesions.

The conclusions arrived at in this communication are based upon an examination of seventy-three neurological cases, of whom fifty-two were suffering from *chronic epidemic encephalitis lethargica*, most of whom presented the typical Parkinsonian syndrome. The remaining twenty-one were patients who had never had encephalitis, some of whom showed manifestations of pyramidal, others of extra-pyramidal, and three of them a combination of pyramidal and extra-pyramidal lesions. The term *chronic encephalitis* is preferred here, for there is increasing evidence to show that many symptoms previously regarded as sequelae

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of the acute disease may really be due to a smouldering and progressive inflammatory process within the brain, in many respects similar to that which occurs in general paralysis.

Description of Condition.

The essential feature of the skin condition here referred to appears to be excessive secretion of sebum. As a result, the skin is unusually greasy and shiny (Plate 9, Fig. 1), and as this is always most noticeable on the face, Cohn gave to it the name 'Salbengesicht'. It is less noticeable on the neck and trunk, and the extremities usually remain unaffected. When well developed the skin of the face is swollen, doughy, and covered with sebum. One frequently receives the impression that some ointment has been applied, and, indeed, a considerable amount of grease may be wiped off with a cloth. The degree to which this is seen varies. Thus, excitement, heat, and sweating, all produce an increase in the greasiness, and the excessive sweating common in post-encephalitic Parkinsonism may in part account for this. In old-standing cases when the secretion of sebum is not very excessive, a scaly eruption on a hyperaemic base is frequently present, particularly over the forehead. This resembles the scaly 'seborrhoid' so commonly seen on the chest in cases not associated with nervous disease. In such cases, a mild degree of blepharitis is usually present. When seen during or within a short time of the acute or pyrexial period, the skin of the face shows a diffuse pink flush, but after a time this tends to diminish or even to disappear completely, when telangiectasis over the cheeks is generally observed. The mouths of the sebaceous glands are unduly conspicuous and wide, and are frequently occupied by black keratinous plugs. In old-standing cases, particularly in the poorer types of hospital patients, the skin, especially of the face, may be covered with a papular, acneiform, or pustular eruption, which may leave numerous disfiguring pits and scars (Fig. 2). These lesions are undoubtedly of a secondary nature, and are probably due to infection of the sebaceous glands with various organisms such as the acne bacillus, or a staphylococcus, &c., a process favoured by the oily surface and predisposed to by neglect.

Pityriasis capitis is almost invariably present. There is always an excessive amount of dandruff, usually dating from the acute illness, but where this was previously present it has, with few exceptions, increased since. Further, the hair is usually very oily and greasy. In long-standing cases the hair tends to fall.

The 'seborrhoeic' skin just described is generally associated with two common manifestations of chronic encephalitis—Parkinsonian rigidity and excessive salivation. With regard to the former, it frequently seems to form an important factor in the production of the typical 'facies'. The swollen and doughy skin accentuates the 'mask-like' appearance, tending to eliminate the finer wrinkles and furrows so essential to expression in the normal individual. This abnormality of the skin was present to a variable degree in forty out of forty-five patients showing the Parkinsonian syndrome, and of these thirty-eight had excessive

salivation. In no case where sialorrhoea was marked was the skin normal, although the converse of this did not hold. In a general way it may be stated that the greater the Parkinsonian rigidity, the more troublesome was the sialorrhoea and the more obviously abnormal was the skin of the face. In three of the patients in whom both excessive salivation and a seborrhoeic skin were observed, excessive secretion from the nose, varying in amount at different times, was also complained of. Not infrequently a change in the skin was first noticed within a few weeks of the acute onset at about the time when muscle stiffness and tremors were first beginning to attract attention. Cohn's (5) original observation was made during the acute stage of encephalitis, and a pink, smooth, and greasy skin was independently noted during the pyrexial period in those of our patients in whom lethargy, catatonia, and a mask-like facies were present from the beginning. As a rule, however, there was a 'latent period' between the onset of these symptoms and the acute attack. As most patients were very vague as to the date of onset of these symptoms, particularly the skin condition, this period was difficult to estimate. In most cases muscular rigidity was first noticed between six and eighteen months after the acute phase, and changes in the skin and hair at about this time. The longest interval between the acute phase and the onset of seborrhoea and Parkinsonism was five years, and this was in a man aged 56. Although this 'latent period' did not seem to show any definite relationship to age, it did appear longer in older individuals. Both the seborrhoea and sialorrhoea appear to diminish with time, and to some extent with the administration of hyoscine or belladonna, even though the muscular disability may remain stationary or get worse. Both sexes are affected equally. Age, however, seems to have considerable bearing on the degree to which the seborrhoeic skin is developed. It is most frequently and noticeably present in the young—most of our patients were between 16 and 30 years of age. According to Sequeira (19) the sebaceous glands are normally most fully developed on the face at the time of adolescence, and this would well explain both the age incidence and the site of affection in our cases.

A number of other abnormal conditions was frequently observed, mostly manifestations of vasomotor disturbance, e. g. hyperidrosis, patchy hyperaemia, blotchiness of the skin, and coldness and blueness of the extremities. These are of interest here in that they indicate involvement of the vegetative nervous mechanism, but since they are not a constant feature of the Parkinsonian syndrome they will be discussed elsewhere.

No definite relation of this peculiar cutaneous abnormality to other post-encephalitic disturbance has been found in the course of this investigation. Stieffler's (20) observation that seborrhoea may occur as the only evidence of chronic encephalitis has not been confirmed here, although it has been seen to a noticeable degree in patients in whom muscular stiffness and facial immobility could only just be detected. This may be partly explained by the fact that most of the patients examined were attending the Out-patient Clinic for neurological symptoms.

The almost constant association with the mask-like facies led to the examination of allied conditions. In six out of eight cases of senile *paralysis agitans,* the face showed a definite seborrhoeic tendency. The skin was smooth, pink in colour, shiny, and at times definitely greasy. It was never so marked as in the cases of chronic encephalitis, but whereas the average age of the latter patients was 25 years, that of the patients with idiopathic paralysis agitans was 58 years. As already shown, age is an important factor. Excessive salivation was present in three of these cases. Unfortunately opportunity did not arise for examining other examples of pure striatal syndromes, such as Wilson's lenticular degeneration.

Several patients having mixed pyramidal and extra-pyramidal lesions, but who were not suffering from chronic epidemic encephalitis, were also examined. When a rigid mask-like facies was present, definite cutaneous changes were seen. Excessive salivation was present in these patients.

Case Reports.

Case VI. G. T., male, aged 51, noticed that during the past four years his upper and lower limbs had been getting increasingly stiff and weak. Later his left hand had begun to tremble. His movements had become slow and difficult. He also complained of occasional headaches, attacks of giddiness, and dyspnoea on exertion. There was always excessive salivation, especially in the early hours of the morning. No previous ill health. On examination he presented the attitude, gait, and facies of a case of early paralysis agitans, with a coarse rhythmic tremor of the left hand. There was definite weakness and 'clasp-knife' type of spasticity in the left upper and lower limbs. The right side of the body was unaffected. The face showed a slight paresis of the upper motor neuron type, on the left side. Cranial nerves were not affected. The tendon reflexes on the left side were exaggerated; those on the right side could just be obtained. There was an extensor plantar response on the left side. The abdominal reflexes were all present, but diminished on the left. Sensation was normal. The brachial and radial arteries were thickened and tortuous, and the fundi showed typical arteriosclerotic changes. The blood-pressure was 185 mm. Hg systolic, and 125 mm. Hg diastolic. The Wassermann reaction of the blood was negative on two occasions. His face, neck, and chest presented a greasy, somewhat thickened, and doughy skin covered with numerous acne papules and pustules. The hair was full of dandruff. The latter manifestations had only become noticeable to the patient since the onset of the other symptoms.

This man with a left hemiplegia obviously had a lesion affecting both the right pyramidal and extra-pyramidal system. No association with any illness suggesting encephalitis could be traced. Syphilis may be excluded by the negative history and negative Wassermann reaction. The abnormal state of the arteries, however, together with the fact that the condition was steadily progressive, would suggest that a vascular thrombosis is the most probable lesion.

Case XXI. E. B., female, aged 32, was attending the Out-patient Department for stiffness and weakness on the left side and 'fits'. These symptoms dated back to an acute illness at 12 years of age, when she was comatose for several days, and after this had 'kidney' trouble with oedema, from which she slowly recovered. There was occasional dribbling from the mouth in the morning. On examination she was slow and stiff in all her movements, had a slightly fixed and expressionless face, and there was weakness and rigidity of all her limbs more especially on the left side. All the deep reflexes were exaggerated, more

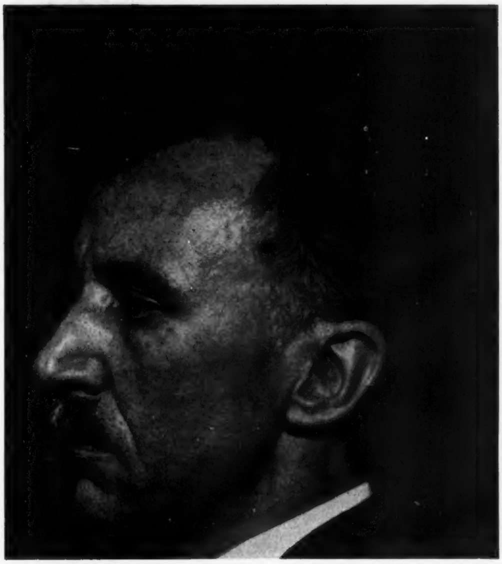

Fig. 1. Showing characteristic greasy and shiny facies of post-encephalitic Parkinsonism.

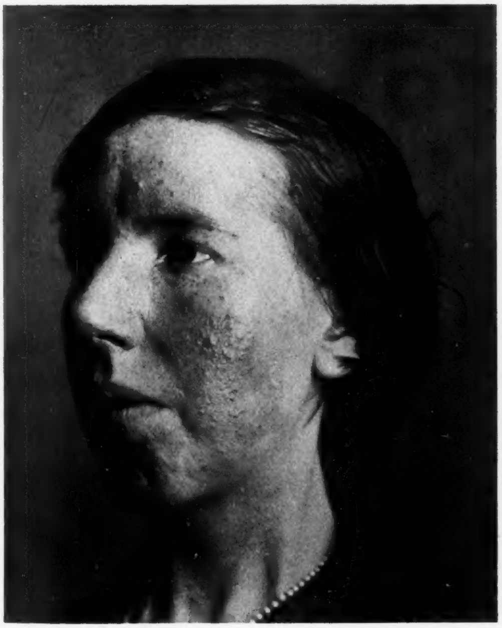

Fig. 2. Case of post-encephalitic Parkinsonism showing acneiform and scarred condition of face.

Fig. 3. To show the shiny seborrhoeic facies in a young patient presenting manifestations of Parkinsonism probably not due to encephalitis lethargica.

so on the left than on the right side, the abdominal reflexes were present but diminished on the left, and a flexor plantar response was present on both sides. She had never been seen by us during one of her 'fits', but it was stated that they consisted of coarse involuntary movements of the left arm and leg, during which consciousness was sometimes lost. The hair was very oily and powdered with scurf. There was an obvious seborrhoeic condition of the face; the skin was greasy, shiny, swollen, and doughy. The mouths of the sebaceous glands were widely open, and the presence of numerous acneiform pustules, papules, and pitted scars had severely disfigured the patient (Fig. 3).

This case illustrates the association of a very obvious 'seborrhoeic' condition in a hemiplegic patient, presenting also manifestations of an extra-pyramidal lesion. This followed an acute cerebral illness sustained twenty years ago. That this was one of the acute specific fevers, possibly diphtheria, is suggested by the history of nephritis following it.

The skin was also examined in other cerebral conditions, e. g. hemiplegia of embolic or thrombotic nature, and in none of these was there any evidence of a 'seborrhoeic' tendency which had appeared since the onset of the neurological symptoms.

Pathology of the Disorder.

We have seen, then, that although this interesting abnormality of the skin is a frequent manifestation of chronic encephalitis lethargica, it also occurs, though to a less degree, in certain other conditions exhibiting the Parkinsonian syndrome. Thus it must be independent of any one specific aetiological factor. The frequent association with conditions presenting Parkinsonian rigidity, however, is more than can be accounted for by mere coincidence. Hence it is reasonable to seek for a common pathological basis to account for both phenomena, and our attention must be especially directed to the neighbourhood of the corpus striatum. This will include a consideration of the thalamus, subthalamic region, floor of the third ventricle, and the substantia nigra.

The secretion of the sebaceous glands is doubtless under the control exercised by the autonomic nervous system. Pathological changes affecting the nervous connexions of these glands at any point between the most central nuclei and the terminal nerve endings would be expected to result in secretory disturbances.

Changes occurring primarily in the glandular substance itself would no doubt be followed by altered secretion—probably tend to complete absence of it—but of this we have no direct evidence. Although the sebaceous glands have not been examined histologically in these cases, the obvious variations in secretion seen during the day—the increase during excitement or on exposure to warmth, the diminution after the exhibition of belladonna or hyoscine, and in some cases simply in the course of time—all point to an interference with nervous control rather than to primary structural changes in the gland substance. In this connexion, it is particularly interesting to note the common association of the 'seborrhoeic' facies with secretory disturbances of other glands in the head having a similar nervous control.

Increased lachrymal secretion is very rare, and was not observed in any of our cases. That this may occur in chronic *encephalitis lethargica* is known, and Claude and Dupuy-Dutemps (4) described such a case. To the occurrence of

rhinorrhoea reference has already been made earlier in this paper. With regard to excessive salivation, all are agreed as to its occurrence in post-encephalitic Parkinsonism, although there is considerable difference of opinion as to its relative frequency. That, like the 'greasy' skin, it occurs in other conditions manifesting the striatal syndrome has already been shown.

There are two prevalent views as to its causation. The first is that it may be due to structural changes within the gland itself. In acute cases of encephalitis lethargica, histological changes were found in the salivary glands, particularly in the parotid by Marinesco (11), Netter, Césari, and Durand (16), and others, but this has not been confirmed in chronic cases. The latter workers have also demonstrated the virus of *encephalitis lethargica* in the salivary secretions of acute cases, but this too has not been repeated in chronic cases. Moreover, actual infection of the glands themselves would not account for the sialorrhoea in such conditions as idiopathic *paralysis agitans*. The second, and more generally accepted view, is that the sialorrhoea is due to an accumulation of secretion within the mouth and pharynx owing to the rigidity and immobility of the buccal and pharyngeal muscles. There are several reasons for regarding this explanation as inadequate. Whereas the degree of muscular rigidity does not tend to show any gross or frequent change, the amount of dribbling may vary considerably, even at different times of the same day. Thus excitement and eating both frequently result in increased salivation, without being associated with any corresponding changes in the muscular state. Administration of atropine or hyoscine, though often reducing the muscular stiffness, quite frequently diminishes the salivary secretion without any corresponding change in the muscle state. Further, as already pointed out, the sialorrhoea shows a natural tendency to lessen with time in many cases in whom the muscular rigidity may actually increase. Finally, it has been observed that attempts at keeping the mouth dry by careful and frequent swabbing of the buccal cavity in several patients having obvious sialorrhoea quite failed—that, in fact, fluid collected in the mouth far more quickly than it did in normal controls. For these reasons I believe that there is a definite increase in the salivary secretion due to abnormal control exercised by the autonomic nervous system.

It has long been recognized that lesions of the central nervous system may be associated with manifestations of vegetative disturbance, as, for example, the excessive sweating in hemiplegia. In considering the question as to the site at which the vegetative nervous system is affected in the condition under discussion, many difficulties are encountered. Not the least of these is the fact that our knowledge of the anatomy of the central and peripheral connexions of the autonomic pathways is still vague and incomplete. Moreover, the exact sites of the lesions in these conditions, are still uncertain. Changes in the sympathetic and parasympathetic connexions outside the brain-stem cannot for certain be excluded. It is at least significant, however, that Lévy (8) found no pathological changes in the sympathetic ganglia in cases of chronic *encephalitis lethargica*. The constant association of secretory disorders of at least two sets of glands, with manifesta-

tions of gross lesions of the brain-stem suggest that the disturbance is probably central. The certain localization of this disturbance must, however, remain impossible, so long as the anatomical distribution and physiological function of the central connexions of the autonomic nervous system is incompletely known. It is known that throughout the brain-stem and cord there are important groups of cells connected with the sympathetic and para-sympathetic nerves. These have characteristic histological features. In the cord they are anatomically distinct, as in the lateral horn of the cervical and dorsal segments. In the medulla and pons, though not so well defined, they are still recognized as characteristic groups of cells associated with the nuclei of the cranial nerves. Passing up the brain-stem they may be traced through the mid-brain to the base of the third ventricle and subthalamic region. Here they are no longer anatomically defined as distinct centres, but are recognized by their histological features, and found to be diffusely scattered with occasional grouping.

It is to those regions where pathological changes are most conspicuous in diseases presenting the Parkinsonian syndrome that our attention must be especially directed.

The Parkinsonian syndrome is generally attributed to pathological changes in the corpus striatum. There is still much uncertainty, however, as to the exact function not only of the various parts of this structure, but also of the surrounding areas. Earlier studies were directed to the immediate neighbourhood of the lenticular and caudate nuclei. More recent investigations, particularly in the case of encephalitis lethargica with its very diffuse lesions, have brought into prominence the part played by the substantia nigra and the structures at the base of the third ventricle. Marinesco (11), McKinley (14), and more recent authors have demonstrated extensive pathological changes in the substantia nigra in cases of post-encephalitic Parkinsonism. In none of these cases were there striking changes in the basal ganglia. McAlpine (12) described two cases of post-encephalitic Parkinsonism, in one of which the maximum changes were noted in the substantia nigra, and in the other the basal ganglia and subthalamic regions were most extensively involved. In both these cases haemorrhages were found in the vicinity of the third ventricle. Although in a more recent paper McAlpine (13) was unable to find any obvious changes in some of the larger subthalamic nuclei, it seems clear that owing to the proximity of this important region to the substantia nigra one would not be surprised at interference with any of its functions.

The clinical features of idiopathic *paralysis agitans* have generally been attributed to lesions of the globus pallidus. More recent investigations have shown that the substantia nigra may be involved. Thus Trétiàkoff (21) and Lhermitte and Cornil (9) have independently described well-marked changes in this part of the brain of such cases. Trétiàkoff (21), moreover, in one of his series, found a unilateral lesion of the substantia nigra in a patient who had suffered from idiopathic *paralysis agitans* with Parkinsonian rigidity on the side opposite to the lesion.

Whatever, then, the exact physiological function of the individual nuclei and tracts of the affected areas may be, it seems clear that the neighbourhood of the pes cerebri and base of the third ventricle must be frequently involved in conditions manifesting the Parkinsonian syndrome.

Much recent work, both clinical and experimental, has directed attention to the importance of the nuclei at the base of the thalamus and third ventricle in connexion with vegetative disturbance. Karplus and Kreidl (7) were able to produce contraction of vessels and secretion of tears by experimental stimulation of a large group of cells in this region—the corpus subthalamicum. Isolated clinical cases have occurred in which traumatic lesions involving these cells have been followed by similar manifestations. Thus Schrottenbach (18) described a case in which disorders of cutaneous secretion resulted. The association of the hypothalamic nuclei with the function of important viscera was demonstrated by Brugsch, Dressel, and Lewy (2). These authors found that secondary degenerative changes occurred in them after destruction of the sympathetic nucleus of the vagus.

Disorders hitherto regarded as resulting from lesions of the pituitary gland have attracted particular attention. In patients presenting the dystrophia adiposa syndrome, Müller (15) found lesions in the floor of the third ventricle or even hydrocephalus of this chamber, although the pituitary gland itself was quite normal. Bailey and Brenner (1) and Camus and Roussy (3) have produced polyuria and glycosuria by experimental lesions of the base of the brain close above the pituitary in which the gland itself was left intact. These facts are not without interest here, for examples of so-called 'dyspituitarism' with dystrophia adiposa, polyuria, and glycosuria are not infrequent in patients who have suffered from encephalitis lethargica. Yet this disease shows no predilection for the ductless glands (22). Of similar importance is the work of Dressel and Lewy (6). They found a definite diminution in sugar tolerance in idiopathic paralysis agitans, a disease in which there is no evidence that the pituitary or other endocrine glands were affected. These authors conclude that the pathological lesions occurring in idiopathic paralysis agitans involve important centres connected with carbohydrate metabolism.

We have seen, then, that in chronic *encephalitis lethargica* and allied conditions manifesting the Parkinsonian syndrome, lesions of a destructive nature are found in the substantia nigra, and in the region of the base of the third ventricle adjoining it. There is considerable evidence that within these areas are important centres connected with the autonomic nervous system. It is possible, therefore, that the frequent association of persistent hyperaemia of the face and excessive secretion of the sebaceous and salivary glands with the Parkinsonian syndrome can be attributed to a disturbance of these centres. Moreover, it is likely that similar centres related to the nasal and lachrymal secretions may also reside in this locality. That the affected nuclei are situated near the median line is suggested by the fact that the seborrhoeic condition is always bilateral, even though the muscular rigidity may be more obvious on one side than the other.

It is impossible to exclude the effect of lesions in other parts of the brain-stem. Mackenzie (10) adduced evidence for regarding the muscular rigidity in chronic *epidemic encephalitis* as due to involvement of the vestibular nucleus in the pons, and points out the proximity of this nucleus to one for the salivary glands. Although the involvement of these centres cannot be denied, lesions in this region in cases of chronic *encephalitis lethargica* and allied conditions are neither so frequent nor so obvious as in the neighbourhood adjoining the base of the third ventricle.

For reasons already stated no attempt has been made to arrive at any definite conclusions concerning the exact localization of the lesion responsible for the disorders described in this paper. Nevertheless it is hoped that the foregoing remarks may still serve some useful purpose in advancing our knowledge of the subject, if only by stimulating further interest in it.

Summary.

1. A seborrhoeic condition of the skin is described as a feature of chronic *encephalitis lethargica* manifesting the Parkinsonian syndrome.

2. The occurrence to a less extent of this cutaneous disorder in other conditions characterized by Parkinsonism, and its association with excessive salivary and occasionally excessive nasal secretion, are pointed out.

3. It is suggested that these secretory disturbances may depend upon lesions in the neighbourhood of the third ventricle involving vegetative nerve centres.

I am indebted to Drs. Lewis Smith, Theodore Thompson, and George Riddoch for kindly allowing me to examine their patients, and for very valuable advice and help.

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ANEURYSMAL DILATATION OF THE LEFT AURICLE[1]

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With Plates 10–12

We have recently had the opportunity of studying a case of chronic rheumatic carditis in which the heart was enlarged to such an extent that it occupied the whole of the lower part of the chest, caused complete collapse of the base of the right lung, and gave rise to an extensive area of dullness in the back. The physical signs and X-ray findings were so similar to those in other cases (1, 10, 16, 24, 25) previously reported in the literature, that there could be no doubt that the great cardiac enlargement was due to extreme dilatation of the left auricle, a diagnosis which was subsequently confirmed *post mortem.*

The clinical history of the case was remarkable. The cardiac lesion dated from a severe attack of rheumatic fever at the age of 10; but for the next ten years, except during occasional intercurrent attacks of bronchitis, the circulatory mechanism exhibited a high degree of efficiency, in spite of the fact that during the whole of this period the patient's occupation entailed strenuous physical work.

Cardiac enlargement had been present from an early age, and at autopsy both ventricles were found to be considerably hypertrophied. The outstanding feature of the case, however, was the extreme dilatation of the left auricle, which was equal in size to the other three chambers of the heart taken together.

Moderate dilatation of one or both auricles is a common finding in chronic rheumatic carditis; but extreme dilatation of the left auricle is very rare. We believe it can only be explained in one of two ways. It must be due either to the presence of some additional factor which predisposes to dilatation, or to the absence of some condition generally present which tends to prevent its occurrence. The lesion described in this paper appears to us to be more than a mere pathological curiosity, for it serves to illustrate certain mechanical principles which have a general application in cardiac pathology.

In addition to our own case we shall refer in detail to the clinical history and post-mortem findings in a second patient who was under the care of Dr. John Cowan, and more briefly to other similar cases, some of which have previously been reported in the literature.

[1] Received May 21, 1927.

[2] Working on behalf of the Medical Research Council.

Case I. A man, 25 years of age, was sent to consult one of us in June, 1926, on account of grave heart failure with a persistent cough, and attacks of severe dyspnoea. Occasionally he had slight epigastric discomfort, but never any praecordial pain or dizziness. There was no family history of rheumatic or cardiac trouble. Up to the age of 10 he had had no illness of any consequence, and was a healthy, lively boy. He then contracted a severe attack of rheumatic fever; an apical systolic murmur developed at that time, and showed no tendency to disappear, despite the fact that he was kept in bed for thirteen weeks and was off school for six months. There was a slight recurrence of the rheumatic pains in the knees in the following year (1912) and again in 1913, but never subsequently.

For several years he kept surprisingly well, and from the age of 11 to 14 he led a strenuous life selling newspapers in the streets. Whilst so employed he experienced no difficulty in keeping pace with his competitors in their daily race to be first on the pitch. At 14 he became a sheet-metal worker, but from time to time was laid off work for short spells with bronchial catarrh and dyspnoea. His doctor states that the heart was gradually growing larger during this period, but his exercise tolerance was but little impaired, and remained so until about the age of 20, when the attacks of dyspnoea became more frequent. The symptoms, however, were always amenable to treatment, and were quickly relieved by a few days' rest in bed with digitalis.

In the summer of 1922 he caught a severe cold watching a cricket match, and developed acute bronchitis followed by haemoptysis. This illness, although it only necessitated his being confined to bed for three or four days, appears to have been the starting-point of more rapid downward progress, and in the following March his heart finally gave way, and he was laid up for five weeks. His firm in consequence transferred him to clerical work, and he remained so employed for the remainder of his life. In spite, however, of this change to a more sedentary occupation, the attacks of dyspnoea recurred at shorter and shorter intervals, and entailed longer and longer rests for their relief. During the last two years of his life, in addition to his previous symptoms, he suffered from tightness of the chest, general weakness, and palpitation, with occasional oedema of the legs. He was a non-smoker and had always observed strict moderation in the matter of alcohol. The Wassermann reaction was negative.

Physical examination. He was a man of very poor physique and feeble muscular development; the contour of the chest was grossly asymmetrical, owing to bulging of the ribs on the left side. There was a moderate degree of cyanosis, but no clubbing of the fingers. At the time of examination no subcutaneous oedema was present either in the extremities or elsewhere, and the veins of the neck were not engorged, even in the recumbent position with his head but slightly raised above the bed. The liver was slightly enlarged, extending just below the costal margin: the spleen was not palpable. The urine was concentrated and gave a heavy cloud of albumin on boiling.

The maximal cardiac impulse was in the 6th intercostal space, its outer limit being seven inches from the mid-sternum. It was heaving and well sustained, producing movement of the 5th, 6th, and 7th ribs. The deep cardiac dullness extended four inches to the right of the sternum in the 4th space, but its upper limit was in the normal situation, and there was no impairment of the percussion note over the manubrium; nor was there any systolic retraction of the chest wall. Both heart sounds were greatly accentuated, the second being reduplicated at the apex, and the first supplemented by a rasping systolic murmur. This murmur was audible all over the front and back of the chest, and was palpable as a coarse thrill, not only in the vicinity of the cardiac impulse, but also in the *right* inframammary region. The resting heart-rate was 90, and its rhythm typical of auricular fibrillation. The blood-pressure, as nearly as could be ascertained in view of the fibrillation, was 160/70. There was no palpable thickening of the

walls of the superficial arteries, and the retinal vessels and fundus oculi were normal. On the posterior aspect of the chest the percussion note on the right side, below the level of the 5th rib, was grossly impaired; vocal fremitus was absent in this region, and the breath sounds were only just audible, while on the left side they were extremely harsh, and moist sounds were present at the base. The throat was healthy, and the teeth were in good condition.

X-ray examination showed enormous cardiac dilatation, the heart shadow with the patient facing the screen (Plate 10, Fig. 1) extending from one side of the chest almost to the other. The opacity of the right side, due to the enormously dilated auricle, was so extensive as to bear a superficial resemblance to the shadow of a pleural effusion. In the oblique position the heart shadow was seen to be separated from the right chest wall by a thin layer of lung. It projected backwards towards the vertebral column, completely filling the retrocardiac clear space. The left border of the heart shadow in its upper part was formed by the auricle. A definite pulsation could be made out in this region. Since the auricles were known to be fibrillating, this pulsation could only be accounted for by passive distension of the left auricle produced by free regurgitation of blood through the mitral orifice during ventricular systole, a hypothesis supported by the wide distribution of the systolic mitral thrill, and subsequently corroborated by the post-mortem findings.

Subsequent progress. The patient was admitted to the Manchester Royal Infirmary on June 15, 1926, and was treated by rest in bed with small doses of digitalis. He appeared to be making very satisfactory progress; the heart-rate slowed down to 70 per minute, he felt well, and was in the best of spirits, when on June 20, suddenly and without warning, whilst using the bed-pan, he fell over, gave a few gasps, and was dead within five minutes, death being due apparently to ventricular fibrillation.

Post-mortem findings. The pericardial sac extended almost to the right chest wall and had caused permanent collapse of the greater part of the lower lobe of the right lung. There were some old fibrous adhesions between the pericardium covering the left auricle and the collapsed lung. Apart from slight emphysema the left lung appeared normal.

The liver (weight 1,500 grm.), spleen (weight 125 grm.), and kidneys (weight 180 and 185 grm. respectively) showed a moderate degree of chronic venous engorgement, but no other macroscopic evidence of pathological changes.

The heart (Plate 11, Fig. 2, and Fig. 3) weighed 900 grm. All its chambers were considerably enlarged, but the left auricle was so greatly dilated that it almost equalled in size the whole of the rest of the heart. This dilatation was not uniform, but affected the right half of the auricle more than the left. Stretching of the upper and posterior wall had given rise to an irregular dome-shaped prominence which projected towards the right, passing above and behind the right auricle and behind the superior vena cava. The left part of the chamber, though also enlarged, retained more nearly its normal form, so that the auricle as a whole was pear-shaped, having its broad base directed towards the right. From the tip of the appendix to the base it measured 20 cm. and the vertical diameter at its broadest part was 14 cm. Its capacity, estimated after the heart had been kept for some days in a fixative solution, was 1,080 c.c. The wall of the left auricle was thickened in most parts. In the left half, and in the lower part of the right half, there was a distinct hypertrophy of the myocardium, but over the dome-shaped prominence above there was irregularity in thickness with some areas of thinning. The endocardium was slightly, but uniformly, thickened over the whole surface. The points of entrance of the four pulmonary veins were abnormally far apart, the wall between them being greatly stretched.

The right auricle and both ventricles were uniformly dilated and hypertrophied. From the tip of the prominence of the left auricle to the apex of the left ventricle measured 24 cm.

The superior vena cava was displaced forward and entered the right auricle near its anterior extremity, while the inferior vena cava entered posteriorly. No destructive valvular lesion was found, but the mitral orifice was much dilated, admitting five fingers. The cusps of the valve were in no way deformed, but were rather larger than normal. The myocardium of the ventricles was free from any inflammatory or degenerative lesion. The coronary arteries, so far as could be ascertained from naked-eye examination, were healthy, though slightly dilated.

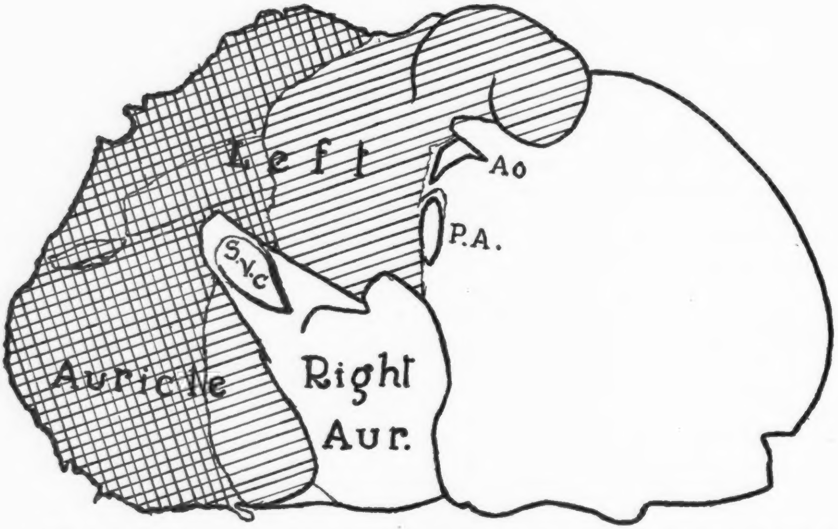

FIG. 3. Outline drawing of Fig. 2. Shaded area is left auricle. Cross-hatched area is portion of auricle to which pericardium was adherent.

S.V.C. = superior vena cava. *Ao.* = aorta. P.A. = pulmonary artery.

In the pericardium there was no excess of fluid. The posterior part of the sac showed some dense fibrous adhesions which obliterated the great oblique sinus and the pockets on either side of it, but these adhesions did not extend below the level of the inferior pulmonary veins. In front, the pericardium was adherent in the upper part of the transverse sinus, but not over an area great enough to close the sinus, which was much wider than normal on account of the enlargement of the left auricle. Thus a large part of the left auricular wall was entirely free from pericardial adhesions. Nevertheless such adhesions as were present were spread over a large area, since the part of the wall which they occupied, namely, the right portion of the upper half of the auricle, was greatly stretched. They covered the whole of the dome-shaped prominence which projected into the right side of the chest (Fig. 3).

Histological examination. Sections were made from various parts of the wall of the left auricle and of other chambers of the heart. They included one, 12 cm. in length, cut from the whole width of the wall, from back to front, passing across the dilated prominence. By coiling this section on a slide it was possible to mount it intact. Microscopic examination showed that in the lower part of the wall of the left auricle, both in front and behind, the myocardium was definitely hypertrophied (Plate 12, Fig. 4), whereas in the upper and more dilated parts, where there were pericardial adhesions, the muscular elements were almost entirely absent and replaced by fibrous tissue (Plate 12, Fig. 5). This was well

shown in the long section, the middle portion of which represented the more dilated part of the auricle. In passing inwards towards the centre, at the point where the pericardial adhesions commenced, the myocardium at first appeared stretched, then separated into thin bundles which gradually tailed out into fibrous tissue, while farther on, towards the centre of the area, no muscle at all was present.

The pericardial adhesions appeared to be of long standing and were completely organized. In the centre of the dilated area the pericardium was so intimately incorporated in the wall of the auricle that it was difficult to make out a line of demarcation between it and the myocardium. For the most part the wall consisted of dense non-cellular fibrous tissue of varying thickness, forming stout parallel laminae in close apposition to the endocardium. The blood-supply of that part appeared to come from the vessels on the outer surface and was probably derived from the mediastinum. No sign of any vascular disease which might have accounted for the myocardial lesion was detected.

Case II. We are indebted to Dr. John Cowan (6) for the clinical history and post-mortem findings in the following case, which he described in fuller detail in his Gibson Memorial Lectures (5).

A woman, aged 27, was admitted to the Glasgow Royal Infirmary in April, 1914, with chronic rheumatic carditis. She had had rheumatic fever in 1899, at the age of 12, and again in 1910, and ever since the first attack she had been short of breath on exertion. She had always been delicate; nevertheless she married, and her first four confinements in 1906, 1908, 1910, and 1911 were uneventful. In 1912 she had pleurisy, and towards the end of her fifth pregnancy, in 1913, she was weak and breathless. Confinement was preceded by a second attack of pleurisy, and followed by phlebitis of both legs and a third attack of rheumatic fever. She was in hospital for a month in the spring of 1914 with catarrh in the chest and orthopnoea. There was, however, no oedema nor congestion in the veins of the neck or abdominal organs, and as soon as the catarrh subsided her symptoms lessened.

She kept fairly well until the spring of 1918, when she again became pregnant, and during the last two months of pregnancy had to be kept in bed. Shortly after confinement she was in hospital for two months, with breathlessness and oedema, after which she remained in fair health for a year, and then contracted a fourth attack of rheumatic fever which lasted for ten weeks. In May, 1920, she awoke one night with intense dyspnoea, which persisted and necessitated her being readmitted to hospital. There was considerable bronchitis, the liver was enlarged and tender, she was jaundiced and had albuminuria.

She kept fairly well until November, 1925, when she had a smart haemoptysis, and the attacks of hepatic pain became much more frequent and more severe. On December 8 the pain was especially bad, and her cough and dyspnoea became worse. She was readmitted a week later, very pale though cyanosed, emaciated, and orthopnoeic. The sputum was blood-stained, and the urine contained a considerable quantity of albumin. Haematuria developed a few days later, and was followed by phlebitis in the right leg, which became oedematous. A fresh haemoptysis occurred on December 24. Four days later the left leg became oedematous. Jaundice developed, and she died on January 5, 1926.

In this case, apart from a short period in 1918 following her last pregnancy, there was no oedema nor venous congestion until the veins of the leg became thrombosed just before death. Nevertheless, mitral stenosis and auricular fibrillation had been known to be present for eleven years. Her chief distress coincided with attacks of bronchitis, which were accompanied by transient cardiac dilatation; but apart from these attacks the size of the heart remained practically unaltered from 1914 till 1924. The spleen was found to be enlarged in 1914 and remained unaltered to the end.

Post-mortem findings. The heart was very much enlarged, and lay almost

horizontally in the chest. A few patches of old pericarditis were present over the ventricles. The right ventricle was very large and its wall hypertrophied. The left auricle was enormous, easily admitting two closed fists. Its walls seemed to be wholly devoid of muscular tissue. The aortic cusps were thickened and shortened by chronic endocarditis. The mitral valve showed a typical button-hole constriction, and the tricuspid also was thickened and narrowed. In addition all three valves showed recent acute vegetations. The aorta and the coronary arteries were healthy. The base of the right lung was collapsed and the overlying pleura greatly thickened. The liver was large, and, in addition to the signs of passive venous congestion, it showed a marked increase in the portal fibrous tissues and some perihepatitis. There was also an early cholecystitis which had involved the serous coat. The spleen showed several infarcts of varying age. The kidney showed a chronic interstitial nephritis in addition to scars of old infarcts.

Discussion.

In many respects these two cases bear a close resemblance to one another; but the most striking anatomical feature which they have in common is the tremendous dilatation of the left auricle. The questions which particularly interested us were, What was the cause of this extraordinary dilatation? why had it affected one chamber of the heart to an extent out of all proportion to the other three? and why had it so far exceeded in degree the dilatation which we are accustomed to find *post mortem* in patients who die of chronic rheumatic carditis? Any specific mechanical influence of the associated valvular lesion may be discounted, for in the one case there was an extreme degree of stenosis, whilst in the other the mitral valve was grossly incompetent: and further, both mitral stenosis and incompetence are of common occurrence, whereas extreme dilatation of the left auricle is very rare. Pericardial adhesions likewise could hardly have played any significant part in the production of this lesion, for in Cowan's case there were only a few scattered patches, whilst in our own case pericarditis was strictly localized, and was confined to the pericardium covering part of the left auricle—that part which formed the dome-shaped prominence projecting to the right. The same is true in five of the other cases recorded in the literature to which we shall refer below. The only obvious structural lesion which appeared to us adequately to account for the dilatation was the fibrosis of the auricular wall.

It is well known that a localized replacement of muscle by fibrous tissue forms the basis of the more common condition of aneurysm of the ventricle, and we believe that the evidence is sufficient to justify us in applying the term '*aneurysmal dilatation*' to the two cases described above. Unfortunately in many of the cases recorded in the literature the wall of the dilated auricle does not appear to have been examined histologically, and consequently we are not in a position to affirm with certainty that such cases are examples of the same condition. We shall therefore consider these cases in three groups: (1) Cases in which the muscular elements of a part of the auricular wall were entirely or almost entirely replaced by fibrous tissue; (2) cases in which the macroscopic appearances at autopsy were similar to those in Group I, but in which there is no

precise statement as to the nature of the lesion; (3) cases which have not come to autopsy, but which on purely clinical grounds appear to be examples of the same condition.

Group I. Cases showing Extensive Fibrosis of the Auricular Wall.

Case III (22). A dressmaker, aged 50, who had had rheumatic fever at 18, and pneumonia at 40, began to suffer from dyspnoea after the menopause at 42. About that time she had an embolic hemiplegia, which cleared up in six weeks. At the age of 50 she was in hospital for a month with dyspnoea of moderate severity. She was very thin and somewhat cyanosed. The heart rhythm was regular and there was neither oedema nor hepatic enlargement. There were moist sounds in the lungs, and on the right side an area of dullness with diminished breath sounds and absence of vocal fremitus. She was readmitted a year later with severe dyspnoea, an enlarged liver, and intense cyanosis, and complained of severe pains in the chest. There was, however, no oedema. The physical signs in the heart and lungs were unchanged. Radiographic examination showed an enormous heart shadow, in shape somewhat suggestive of a pericardial effusion. She made a good recovery and was discharged from hospital, only to be readmitted a few days later *in extremis*.

Post-mortem examination. The pericardium was adherent to the upper but not to the anterior surface of the heart. At the base of the right lung, near the mediastinal surface, was a caseous abscess about the size of a hazel-nut. It was encysted by a fibrous shell of pleura more than a centimetre in thickness. The shell was inseparable from the wall of the left auricle, which was moulded into the lung and adherent to it over a considerable area in the region of the pulmonary veins. The left auricle was greatly dilated, its capacity being 400 c.c. It passed behind the great vessels and the right auricle, and formed the right border of the heart. In contrast, the size of the right auricle and of the ventricles was almost normal. The mitral valve was the only one which presented any lesions. Its cusps were adherent, forming a sclerosed ring, which was rigid but not much constricted.

The wall of the left auricle was very thin, white, and fibrous; histologically it showed mere traces of muscle fibres, separated from one another by dense fibrous tissue. Where the auricular wall was directly continuous with the fibrous shell formed by the lung and pleura, the common lesions of fibrous tuberculosis were present.

It seemed probable that the tuberculous process had invaded the auricle which was previously somewhat dilated, destroying the muscular elements of its wall, and transforming it into a fibrous sac which was no longer capable of resisting the intracardiac pressure.

Case IV (23). A man who had had two attacks of rheumatic fever in childhood, and had been somewhat short of breath on exertion since pneumonia four years previously, was admitted to hospital at the age of 18 on account of dyspnoea. There was considerable hypertrophy of the left ventricle, with a heaving impulse and a loud systolic murmur, but no signs of failure, and the heart rhythm was regular. He improved rapidly with treatment, but shortly after discharge had a sudden relapse and was readmitted in a critical condition, with severe palpitation, auricular fibrillation, a heart rate of 170, and intense dyspnoea. The liver was enlarged and tender, there was congestion of the bases of the lungs, but no oedema. The temperature was 38·5° C. Radiographic examination showed a striking alteration in the right heart border (Fig. 6), and the long axis of the heart shadow, which previously measured 17·5 cm., was now 19·5 cm.

His symptoms were relieved by digitalis, but the improvement was not maintained, and he died three weeks later.

Post-mortem examination showed an acute mural endocarditis and an old mitral lesion. The vegetations were extremely friable, and consisted almost entirely of leucocytes with very little fibrin. A shower of small emboli had been thrown off, and many of these had lodged in the auricular branches of the coronary arteries, involving especially those supplying the left auricle, and giving rise to numerous small haemorrhagic infarcts on the sub-endocardial surface of the heart. The right auricle and ventricle showed little abnormality. The left auricle, on the other hand, was very greatly enlarged, its capacity being 250 c.c. Passing behind the right auricle it appeared on the right border of the heart, and was pressing on and adherent to the right lung.

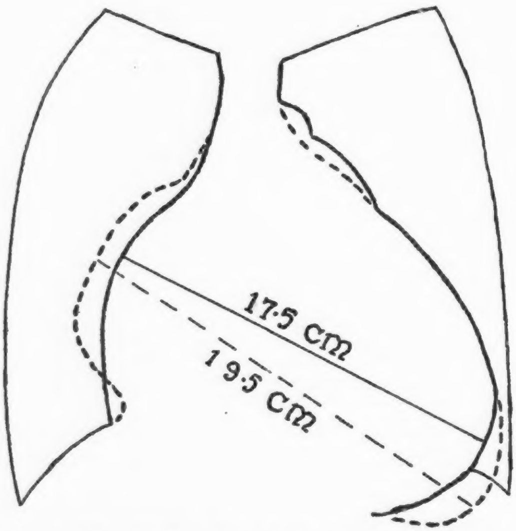

FIG. 6. Orthodiagram of Case IV from Lutembacher's paper. Continuous outline as seen on first admission; dotted outline as seen on second admission to hospital.

The auricular wall for about a finger's breadth above the *a.-v.* groove was normal in colour, consistency, and thickness; but above this level it was whitish, fibrous, and very thin, and in its upper part devoid of muscular tissue. Covering the upper pole of the auricular aneurysm, which had embedded itself in the lung, were firm pericardial adhesions; but elsewhere there was no sign of pericarditis. The mitral orifice admitted three fingers and showed no evidence of recent inflammation.

This case is extremely instructive. It gives a very clear picture of one way in which a fibrotic lesion of the auricular wall may arise. Had the onset been less acute, the endocarditis might have healed, as it sometimes does (20), and the patient survived for a sufficient length of time to admit of further dilatation, such as occurred in the other cases enumerated above.

It is curious that the lesions should have been so localized, and that the wall of the right auricle, as well as that part of the wall of the left auricle adjacent to the *a.-v.* groove (as in our case), should have escaped with so little damage. The distribution of the embolic process suggests that the limits of the affected area must have been determined by the anatomical disposition of the branches of the

coronary artery, and it seems likely that a similar anatomical factor may be responsible for determining the peculiar distribution of the lesions in some of the more chronic cases.

Case V (23). A man, 18 years of age, with a history of dry pleurisy five years previously, was admitted to hospital in May, 1915, and again in September, 1917, suffering from shortness of breath with praecordial pain. He was thin, pale, cyanosed, and of poor physique, with clubbing of the fingers, systolic retraction of the chest wall, and other signs suggestive of tuberculous mediastino-pericarditis. He had auricular fibrillation and a large hard tender liver. X-ray examination showed an auricular aneurysm projecting into the right lung. The apex of the heart was replaced by a blunt inferior border giving rise to the typical *cœur en sabot*. The long axis of the heart measured 20·5 cm.

Failure was progressive, digitalis treatment was badly tolerated, and he died at the end of January, 1918.

Post-mortem examination showed the pericardium to be universally adherent to the heart and adjacent structures. Embedded in the right lung was a portion of the left auricle, projecting 4 cm. beyond the right border of the right auricle. The capacity of the left auricle was 500 c.c., while that of the right auricle was 190 c.c. The wall of the aneurysm was thin, white, and fibrous; and in the region where it projected beyond the right auricle all traces of muscular tissue had disappeared. The wall of the right auricle, on the other hand, though thin and transparent, showed little histological abnormality. The ventricles were hypertrophied but not dilated. The mitral orifice admitted four fingers.

Case VI (8). A woman, aged 32, who had rheumatic fever at 16, frequent minor attacks of rheumatism subsequently, and pneumonia with pleurisy at 21, was admitted to hospital in 1920 with pain in the right chest. She was thin, cyanosed, and dyspnoeic. Physical examination revealed mitral stenosis with auricular fibrillation, moderate cardiac enlargement with dullness extending 1 inch to the right of the sternum, and slight bulging of the left chest. At the right base there was pleural friction, the breath sounds were poor, and the percussion note was impaired. Her symptoms were relieved by digitalis. She was again in hospital in February, 1922, with acute bronchitis, but made a good recovery. In November, 1925, the cardiac dullness extended two inches to the right of the sternum, and two inches beyond the left mid-clavicular line. On her third admission to hospital, in January, 1926, again suffering from bronchitis, the dullness was found to extend three inches to the right of the sternum, and to the left anterior axillary line. She collapsed and died soon after admission.

Post-mortem examination. The pericardium was thickened and its two layers were adherent to one another and to adjacent structures. The heart weighed 31½ oz. Its maximum diameter was 10½ inches. The capacity of the right auricle was half a pint, and its wall showed considerable fibrosis. Both ventricles were hypertrophied, and the right also considerably dilated. The mitral valve was stenosed. The left auricle was enormously dilated, having a capacity of 1½ pints. It projected beyond the right auricle and formed the right border of the heart. Its wall was everywhere very thin, and histologically showed very little muscle and much fibrous tissue.

Case VII (16). An engine-driver, aged 60, of alcoholic habits, who had never suffered from rheumatism or any acute illness, was admitted to hospital with oedema of the legs of ten years' duration. For twelve months he had been short of breath and sleepless, and had suffered from cough for three weeks. He had had an embolic hemiplegia five months previously.

The apex-beat was situated in the 6th space in the mid-axillary line. There was no dullness to the right of the sternum. The pulse was rapid, small, and

'unequal'. He developed double basal pneumonia, and died thirteen days after admission.

Post-mortem examination showed the pericardium to be adherent to the sternum and to both pleurae. Its two layers were universally adherent and much calcified. It was separated from the heart by a thick layer of fat, and three unabsorbed effusions of blood. The cavities of the ventricles were about normal in size. Those of the auricles were enormously dilated, more especially the left auricle. The right would contain both ventricles easily, whilst the left would contain the other three chambers of the heart together. The long axis of the left auricle measured 18 cm., and that of the right auricle 10 cm. The free border of the mitral valve was a little thickened, and the other valves were quite healthy. The auricular walls were so thin that one could read print through many parts of them. A large extent of the auricular walls contained no muscle whatever, but the musculi pectinati were fairly well developed.

Case VIII. A heart showing aneurysmal dilatation of both auricles is preserved in the Pathological Museum at University College Hospital. We are indebted to Sir Thomas Lewis for calling our attention to it.

A bedstead maker, aged 40 years, who suffered from rheumatic fever at the age of 20, and had repeated subsequent attacks, was admitted to hospital with signs of general congestion and dropsy. There was a diffuse cardiac impulse situated in the 5th, 6th, and 7th interspaces, and extending out to the mid-axillary line. Loud systolic and diastolic murmurs were audible all over the praecordium and the auricles were fibrillating.

Post-mortem examination showed congestion of the internal organs with dropsy, hydrothorax, and ascites. The heart weighed 27 oz. and was enormously enlarged, mainly owing to dilatation of the auricles. The two layers of the pericardium were universally adherent. The right auricle was much dilated and its walls were thinned. The tricuspid valve was incompetent. Both ventricles were dilated and hypertrophied. The mitral cusps were thickened and shrunken, but the mitral orifice admitted the tips of three fingers. The left auricle was enormously dilated and had a capacity of about 1½ pints. Its wall was very thin and in its upper part devoid of muscular tissue. The trachea was compressed and displaced to the right, and part of the middle and lower lobes of the right lung were collapsed from pressure of the auricles. The aorta and coronary arteries were healthy.

Group II. Cases in which the Precise Nature of the Lesion is not stated.

Case IX (24). A woman who had a severe attack of rheumatic fever in childhood, and had suffered from rheumatism on subsequent occasions, was first admitted to hospital at the age of 28, with palpitation and dyspnoea of six years' duration. She was well nourished. The apex-beat was two inches below and half an inch to the left of the nipple, but no extension of the cardiac dullness to the right of the sternum was noted. She was discharged after three weeks, much improved; but the pulse, which on admission had been very irregular, still remained so.

Ten years later (aged 38), after an attack of bronchitis with influenza, she was again in hospital for a month with cough, dyspnoea, and pain in the epigastrium and praecordium, radiating down the left arm. In the interval she had had occasional haemoptyses, and her last three pregnancies had had to be terminated prematurely, on account of cardiac symptoms. She was sallow and orthopnoeic. The apex-beat was in the 7th space in the mid-axillary line. There was pulsation in the 4th right space, and a systolic thrill just below the right nipple. The right chest was dull up to the level of the 4th rib in front, vocal fremitus was absent, and breath sounds were deficient in this area. The liver was greatly enlarged, but there was no oedema.

Again her symptoms were relieved by treatment, and she remained fairly well for 2½ years, when she developed severe heart failure with ascites and extensive oedema. The apex-beat was now in the 8th space in the posterior axillary line. The right side of the chest at the back was dull from the level of the 6th dorsal spine to the base, and pulsation could be felt over an extensive area of the right chest anteriorly as far as the mid-axillary line. The patient died a few days after admission to hospital.

Post-mortem examination showed that the pericardial sac, which lay with its long axis transversely, occupied the entire thoracic cavity below the level of the 4th rib, and measured 10¼ inches across. There was no general pericarditis, but posteriorly the two layers were firmly adherent over the left auricle. Both ventricles were moderately hypertrophied and dilated, and the right auricle was considerably dilated. These three chambers all occupied their normal relative positions. The left auricle was enormously dilated and extended 4½ inches beyond the right border of the right auricle. Its capacity was 30 oz., and its greatest diameter 6¼ inches, exclusive of the appendix, which was also greatly dilated. The auricular wall was remarkably thin, and in places translucent, but appeared healthy to the naked eye, and microscopically 'no active morbid processes were found'. The mitral orifice admitted four fingers. The lungs were small and confined to the upper part of the thoracic cavity, the lower lobe of the right lung being collapsed and strongly adherent to the pericardium.

Case X (25). A married woman, aged 27, who had been under treatment for mitral disease for five years, was admitted to hospital with severe dyspnoea, oedema, and cyanosis. The action of the heart was irregular and tumultuous, the apex-beat, which a year previously had been in the 8th space 2 in. outside the nipple line, was now in the mid-axillary line, and the heart dullness extended slightly to the right of the sternum.

The post-mortem report was as follows: The left auricle is larger than the rest of the heart taken together, and is equal in size to two closed fists. Its walls are very much thinned and contain calcareous plates. The appendix is slightly, if at all, dilated. The upper part of the auricle shows the remains of fibrous adhesions resulting from localized pericarditis. The mitral valve is thickened, but not appreciably stenosed. The left ventricle is dilated and hypertrophied, the right auricle moderately dilated. The right ventricle is markedly hypertrophied. The lungs are extremely emphysematous.

Case XI (10). A married woman, aged 44, with a history of growing pains in childhood, had suffered from bronchitis each winter since hysterectomy in 1908 (aged 34), and from shortness of breath on exertion since nephropexy in 1912. She had an embolic hemiplegia in 1914, had been subject to paroxysms of palpitation since 1915, and was in hospital for a month in the autumn of 1918, with cardiac failure and auricular fibrillation.

There was a heaving cardiac impulse in the 8th space in the mid-axillary line, a systolic thrill palpable at the apex and also outside the right mamma, and murmurs of mitral stenosis and tricuspid incompetence. For three years she was able to get about; but in November, 1921, she became bedfast, and was readmitted to hospital in May, 1922, with extensive oedema and advanced heart failure, and died two days later.

At autopsy, only a thin layer of lung was found separating the pericardium from the chest walls on either side. There were dense pericardial adhesions over part of the left auricle. The transverse diameter of the heart measured 12 inches. The left auricle, which had a capacity of 40 oz., protruded 2 inches beyond the right border of the right auricle; its walls were greatly thinned. The capacity of the right auricle was 20 oz. There was moderate hypertrophy of both ventricles, the right being also dilated. There was stenosis of the mitral and dilatation of the tricuspid orifices.

Dr. Emanuel (11) informs us that in this case the auricular wall was not examined histologically, but that to the naked eye it looked like a thin fibrous membrane apparently devoid of muscular tissue.

Case XII (1). An unmarried woman, aged 26, with a history of pneumonia, pleurisy, and rheumatic carditis 14 years previously, was admitted to hospital in June, 1921, suffering from cough, shortness of breath, and praecordial pain. Examination revealed enlargement of the heart to the left but not to the right, mitral stenosis, and auricular fibrillation, with consolidation of the left base.

In the spring of 1923 she had haemoptysis and was again in hospital for twelve days. The cardiac dullness now extended beyond the right mid-clavicular line. A systolic murmur, and pulsation, were present in this region. The spleen and liver were enlarged, but there was no oedema.

X-ray examination showed a large rounded shadow in the right chest, which extended backwards nearly to the vertebral column, pressed on the oesophagus, and displaced the trachea to the right. Its upper margin pulsated. The patient died January 11, 1924.

Post-mortem examination showed general hypertrophy and dilatation of the heart, but the left auricle was dilated out of all proportion to the other chambers. Its capacity was 30 oz. It had compressed and caused collapse of the lower lobe of the right lung. The two layers of the pericardium were universally adherent. The mitral valve was stenosed, and the margins of its cusps thickened and rigid.

Dr. Batty-Shaw states in his paper that he has another similar case in a woman aged 60 under observation.

Case XIII (28). A man, 53 years of age, with a history of multiple articular rheumatism and influenza, was admitted to hospital with cardiac insufficiency, mitral stenosis, high blood-pressure, and auricular fibrillation. The heart dullness extended far to the right and slightly to the left of the normal limits. The percussion note from the right axilla to the mid-clavicular line was tympanitic, and in this region the breath sounds were diminished and the vocal fremitus impaired. X-ray examination showed enormous enlargement of the heart to the right, with collapse of the right lung, the outline of the heart shadow resembling that of a pleural effusion.

Post-mortem examination showed extreme mitral stenosis with healed endocarditis, and great enlargement of left auricle, causing pressure collapse of the right lung.

Case XIV. For the particulars of the following case we are indebted to Sir Thomas Lewis.

A woman of 29, who had chorea at 5 and again at 10 years of age, had been short of breath for thirteen years, and had shown signs of heart failure from time to time during the past nine years, came to hospital with general congestion. The cardiac impulse was in the 6th space in the mid-axillary line. There was a visible impulse over the whole praecordium up to the 3rd space, but no special signs of auricular enlargement and no paralysis of the left vocal chord. She had mitral stenosis and auricular fibrillation.

Post-mortem examination. The pericardial cavity was universally obliterated by soft adhesions. Both pleurae were adherent. The heart weighed 34½ oz. The right ventricle was greatly hypertrophied and the left to a lesser degree. The left auricle was dilated to an extreme extent, and its walls were not much thicker than paper; the right auricle was almost, but not quite so greatly dilated. The right auricular appendix was massive and its muscle greatly increased. The tricuspid valve was enlarged and thickened at the edges.

The Cause of Extreme Dilatation.

So far as the general appearance of the heart is concerned, there is a very striking similarity between many of the cases enumerated above; but, in order to make our premises the more secure, we have thought it advisable to classify them in two groups in accordance with the structural changes found in the auricular wall. In so doing we may perhaps have erred on the side of caution; for, whereas in all the eight cases comprising our first group it is definitely stated that the muscular elements of a part of the wall of the affected auricle had completely or almost completely disappeared, the same may also have been true of the six cases of our second group. In the latter unfortunately the reports do not contain any specific statement to that effect, and it is for that reason that we have decided to place them in a separate category.

The associated pericarditis. There is another way in which these cases might have been classified. In six instances (see Table I) the condition was associated with an extensive pericarditis, whereas in the other seven cases [3] such pericarditis as was present was confined to a strictly limited area of the wall of the left auricle, an area which in our own case corresponded closely to that in which the fibrosis of the myocardium was most pronounced.

The localized pericarditis, such as was present in these cases, closely simulates that which frequently occurs in association with aneurysm of the ventricle, and has been described by many writers (3, 4, 7) on this subject. It is probably analogous to the pleuritic adhesions overlying a superficial tuberculous focus in the lung. During life a localized pericardial rub may often be detected in cases of ischaemic necrosis of the ventricle following coronary occlusion. In fact, it has come to be regarded as one of the most valuable signs in the diagnosis of that condition (13, 19, 32). The lesion has been termed by Sternberg (29) 'pericarditis epistenocardica', and is undoubtedly secondary to the underlying myocarditis. If, as we believe, the localized pericarditis in the cases described in this paper is of a similar nature, it could not have played any significant part in the production of the auricular dilatation; but in the four cases where the pericardium was universally adherent, it is not possible to exclude entirely the influence of mechanical factors. We are inclined to think, however, that even in these the essential lesion, as in the other group, was probably a fibrosis of the auricular wall.

A moderate degree of dilatation of the auricles is a frequent accompaniment of chronic pericarditis; but it is quite exceptional for the auricle to attain such enormous dimensions as are recorded in the cases described above. Even when the adhesions to adjacent structures are very extensive, extreme dilatation of the auricles, and especially of the left auricle, is uncommon. From a consideration of the 25 cases of indurative mediastino-pericarditis reported in his monograph,

[3] In the report of one case (XIII) there is no statement as to the presence or absence of pericarditis.

TABLE I.

Case.	Author and Reference.	Sex.	Age at Death.	Probable Aetiology.	Capacity of Left Auricle.	Pericarditis.	Mitral Valve.
I	Bramwell and Duguid	M	25	Rheum. fever, aged 10	1080 c.c.	Confined to L. A.	Incomp. (5 fingers)
II	Cowan (5 and 6)	F	38	Rheum. fever, aged 12, 22, 25, and 31	Two closed fists	A few scattered patches	Button-hole stenosis
III	Lutembacher (22)	F	51	Rheum. fever, aged 18. Tb., pulmonary abscess	400 c.c.	Confined to L. A.	Sclerosed and incomp. (2 fingers)
IV	Ibid. (23)	M	·18	Rheum. fever twice in childhood	250 c.c.	Confined to L. A.	Incomp. (3 fingers)
V	Ibid. (23)	M	20	Tb., mediast. pericarditis. Pleurisy, aged 13	500 c.c.	Universally adherent	Incomp. (4 fingers)
VI	East (8)	F	38	Rheum. fever, aged 16	30 oz.	General adhesions	Stenosis
VII	Jones (16)	M	60	Obscure	Contain others, 3 heart chambers	General adhesions. Much calcified	Free border slightly thickened
VIII	Lewis	M	40	Rheum. fever, aged 20	30 oz.	Universally adherent	Cusps thickened and shrunken. (Tips of 3 fingers)
IX	Owen (24)	F	40	Rheum. fever in childhood	30 oz.	Confined to L. A.	Incomp. (4 fingers)
X	Owen and Fenton (25)	F	27	? Rheumatic	2 closed fists	Confined to L. A.	Thickened, but not stenosed
XI	Emanuel (10)	F	48	Growing pains in childhood	40 oz.	Confined to L. A.	Stenosis
XII	Batty-Shaw (1)	F	28	Rheum. fever, aged 12	30 oz.	Universally adherent	Stenosis
XIII	Schott (28)	M	53	Rheum. fever	'Enormous enlargement'	Not stated	Extreme stenosis
XIV	Lewis	F	29	Chorea, aged 5 and 10	Greatly dilated	Universally adherent	Stenosis

Harris (15) concludes that this condition is generally associated with cardiac enlargement, but that such enlargement tends to involve the right side of the heart more than the left.

Considerations such as these tempt one to question the validity of the hypothesis that great cardiac enlargement is ever *primarily* attributable to the presence of adhesions. There can be no doubt that one of the most important functions of the pericardium is to reduce to a minimum friction between the heart and adjacent structures. Further it is quite clear that the heart is working at a mechanical disadvantage in the presence of extensive pericardial adhesions, especially when such adhesions anchor it to adjacent organs. On the other hand, extensive pericarditis of long standing is invariably associated with some degree of myocarditis, and chronic myocarditis is bound to weaken the heart wall. It is therefore exceedingly difficult to assess the respective importance of the pericardial and the myocardial factors in the evolution of cardiac enlargement in these cases. Although we are fully prepared to admit that a chronic pericarditis is one factor, the thesis that it is the most important factor in the production of cardiac enlargement is, we submit, 'not proven'.

The myocardial fibrosis. In our case there was an advanced fibrotic lesion of the myocardium of the left auricle, confined, it is true, to a part of the wall of that chamber. The fibrosis involved an area which was also the seat of pericarditis. From histological examination alone, it is not possible to say whether the pericarditis was primary or, as suggested above, secondary to the myocardial lesion. However this may be, the process resulted in complete destruction of the muscle in the affected part of the auricular wall, and on this fact we believe rests the explanation of the great enlargement of the auricle.

The tissue in the wall of the auricle is designed to withstand stretching, and this property is largely dependent on its muscular elements. Muscle is highly elastic; it is capable of being stretched and still retaining the power of recoiling to its original length after the stretching force is withdrawn. There is, however, a limit to its extensibility, and stretching beyond that limit results in permanent structural damage which impairs its ability to recoil.

Under normal circumstances the intra-auricular pressure is not sufficient to stretch the healthy muscle beyond its limit. In addition to muscle, the wall of the auricle contains fibrous tissue, but fibrous tissue has a very small degree of elasticity as compared with muscle. When it is stretched its limit of extensibility is soon reached; and, when a tissue is being repeatedly stretched to the limit of its extensibility, it tends to become permanently lengthened. Normally, stretching of the fibrous tissue is prevented by the muscular elements in the auricular wall. In our case the muscular elements in a considerable part of the wall of the auricle had been completely replaced by fibrous tissue, and the safeguarding influence of the muscle was removed. The anatomical relations of the pulmonary veins show that extensive stretching had taken place in that part of the wall where the muscle was replaced by fibrous tissue. This fibrous tissue was continually being stretched to the limits of its extensibility, and so tended to become

permanently and increasingly lengthened. A similar result is constantly seen in the wall of an arterial aneurysm or in an aneurysm of the ventricle, and it seems probable that this is the nature of the change which had occurred in the cases we are discussing.

It is the ability to recoil after stretching that differentiates physiological from pathological dilatation. Starling (26) and his associates have shown that the healthy heart normally dilates during diastole when the venous inflow is increased, but that it is still able to empty itself during systole. When, however, the output of the heart fails to keep pace with the venous inflow dilatation has passed from the physiological to the pathological category.

When the fibrosis is confined to a small area of the auricular wall it may fail to give rise to any physical signs recognizable during life. The following cases, for the report on the first of which we are indebted to Dr. John Cowan (6), are examples in point:

Case XV. A woman, aged 25, who gave a history of subacute rheumatism at 14, and who was suffering from mitral stenosis with embolic hemiplegia, died a few days after admission to hospital. Post-mortem examination showed a normal pericardium with slight cardiac enlargement due to dilatation of the auricles, especially the left auricle, which was hypertrophied as well as dilated. Above the stenosed and calcareous mitral valve was a small aneurysmal pouch, the wall of which was devoid of muscular tissue. Extensive embolic infarctions of varying age, due to obstruction of small branches of the renal artery, were present in both kidneys; and it seemed probable that the localized fibrosis in the auricular wall which had resulted in the formation of the small aneurysm had been produced in a similar way.

Case XVI. Laforgue (17) records the case of a young Arab with congenital syphilis, who died of malignant malaria. Post-mortem examination showed an aneurysm of the left auricle the size of a walnut. The lesion was due to a gumma having formed adhesions with the pericardium.

The intra-cardiac pressure. In studying the cases of extreme dilatation of the left auricle recorded in the literature, one cannot fail to be impressed by the fact that the condition is so constantly associated with great ventricular hypertrophy. This we believe to be a factor second only in importance to the fibrosis of the auricular wall in the production of this remarkable lesion.

If aneurysmal dilatation depends primarily on a chronic ischaemic fibrosis, strictly confined to a part of the auricular wall, the mechanical factors tending to produce dilatation will be very different from those which prevail where there is a more diffuse lesion involving both auricle and ventricle. In our own case the ventricular muscle apparently escaped practically undamaged, and in most of the cases enumerated above it was greatly hypertrophied. Consequently, the cardiac output is well maintained. Unlike the patient with a badly damaged ventricle who is compelled by limitation of his cardiac reserve to lead a sedentary life, the patient with a healthy ventricle is capable of undertaking severe physical exertion despite his fibrosed auricle. In the latter case the ventricular output, and consequently the venous inflow to the heart, is very much greater than in the former; and, in addition, if the mitral valve becomes incompetent,

blood is poured into the auricle from the ventricle as well as from the pulmonary veins. Both factors which tend to produce dilatation are present, the passive factor—the fibrosis of the auricular wall, and the active factor—the increased auricular inflow.

When, however, the distribution of the lesion is not localized but diffuse, affecting the ventricle as well as the auricle, the cardiac output is reduced, as the result of ventricular insufficiency. It tends to become more and more reduced as the ventricle experiences greater and greater difficulty in meeting its liabilities. The tendency of these two factors, the widespread character of the lesion and the failing ventricle, is to produce, not extreme dilatation of one particular chamber of the heart, but general circulatory insufficiency leading ultimately to death.

In our case X-ray examination showed that although the auricle was fibrillating it exhibited definite pulsation. That this part of the heart shadow did actually represent the auricular appendix, and not the pulmonary artery, was corroborated by the anatomical relations found *post mortem*. This pulsation could only be accounted for by passive distension of the auricle by free regurgitation from the ventricle, and we are therefore forced to conclude that ventricular systole was responsible for producing a definite rise in intra-auricular pressure, and that mitral regurgitation played some part, in the latter stages at any rate, in stretching the auricular wall, and was instrumental in aggravating the conditions which had originally led to dilatation.

There is no need to emphasize the fact which has long been familiar to morbid anatomists, that whereas sudden stoppage of the blood-supply leads to necrosis, a more chronic ischaemia results in fibrosis. As A. G. Gibson (12) stated in a recent paper dealing with the results of coronary occlusion in the ventricle, 'If the occlusion be slow it is probable that fibrous tissue replaces the muscular tissue gradually without the intervention of a stage of necrosis which could be recognized by the naked eye'.

The term 'horizontal dilatation' of the left auricle which has been used by some writers (1, 24) who have previously described cases similar to our own is an apt descriptive term, for it indicates that the dilatation has taken place in an unusual direction, and the peculiar shape of the auricle is one of the most characteristic features in these cases. In our case it is the fibroid portion of the auricle which exhibits the most striking deformity, whereas the remainder of the chamber, including the appendix, where the wall shows little or no fibrosis but considerable muscular hypertrophy, though greatly dilated, has retained more nearly its normal shape.

The localized distribution of the fibrosis in these cases suggests that the lesion is due to a defective blood-supply and is comparable to the more acute process of infarction of the auricular wall which occurred in Case IV: but, whatever be the mechanism of its production, the post-mortem findings prove definitely that in these cases the fibrosis is strictly localized. Gross (14) states that the auricular branches of the coronary arteries are less constant in their

distribution than those which supply the ventricle. It is possible that some peculiar anatomical disposition of these vessels may account for the unusual distribution of the lesion we are discussing.

Group III. Cases which have not come to Autopsy.

In the following cases there can be little doubt that the cardiac lesion is very similar to that described above.

Case XVII (28). A man, aged 29, with a gunshot wound of the left ventricle was admitted to hospital in 1914. He was found to have mitral incompetence, which Schott suggests was of traumatic origin. Until 1918 he was able to carry on his work as a locksmith. He then contracted influenza, and on readmission to hospital was found to have mitral stenosis and auricular fibrillation. X-ray examination showed enlargement of the left ventricle and right auricle, with a bullet embedded in the wall of the left ventricle. In 1922 the subdivision of the right border of the heart shadow into an upper and lower segment was apparent, while in 1924, following an attack of bronchitis, the heart dullness was found to extend from the left anterior axillary to the right mid-clavicular line, and the shadow of the left auricle reached to the right chest wall, and formed the entire right border of the heart.

Two patients with extreme dilatation of the left auricle were shown at a recent meeting of the Clinical Section of the Royal Society of Medicine by Dr. D. Evan Bedford (2).

Case XVIII. A machinist, aged 35, had suffered from dyspnoea on exertion since haemoptysis twelve years previously. There was no rheumatic history. On admission to hospital she was found to have mitral stenosis, aortic incompetence, and auricular fibrillation. There was a systolic pulsation in the right axilla, and radioscopy showed extreme enlargement of the heart shadow, which extended almost to the right chest wall.

Case XIX. A clerk, aged 21, had had growing pains in childhood and heart trouble since the age of 7. She had had heart failure at 14, and at 21 complained of breathlessness, palpitation, and pain under the left breast. Examination showed mitral stenosis, aortic incompetence, and auricular fibrillation. The pericardium was probably adherent, but there were no signs of heart failure. In the right axilla in the 4th and 5th interspaces there was a forcible systolic pulsation, and at times a systolic thrill. Radioscopy showed that the heart shadow extended almost to the right chest wall.

Case XX (27). A shop assistant, aged 32, with no history of acute rheumatism or chorea, had been somewhat short of breath since an attack of pneumonia at the age of 23 in 1911. She first came under observation when suffering from influenza in October, 1919, and was again compelled to seek medical advice in February, 1922, on account of palpitation, nocturnal dyspnoea, and swelling of the feet. She was very thin and cyanosed, and dyspnoea was easily provoked. The apex-beat was very forcible and situated in the 7th space. The heart dullness was increased in all directions, extending 11 cm. to the left and 6 cm. to the right of the middle line. The heart-rate was 120, and its rhythm regular. There was evidence of mitral incompetence and slight stenosis. The Wassermann reaction was negative. She improved with treatment and was able to resume her work in April, 1922. When seen a year later her general condition was much the same.

Radiographic examination in July, 1922, showed that the upper part of the heart shadow bulged far to the right, and extended backwards into the retro-cardiac space, as far as the vertebral column; forming what appeared to be a definite aneurysm of the left auricle.

Exercise Tolerance.

A surprising feature in many of these cases is the comparative well-being of the patients for several years after extensive cardiac damage must already have been established. In our case there can be no doubt that the foundations of the cardiac lesion were laid by the first attack of rheumatic fever, whilst the great deformity of the chest bears witness to the fact that considerable cardiac enlargement had occurred at an early age. Notwithstanding this, however, for ten years, with the exception of occasional short periods of ill health attributable to bronchitis, the circulatory mechanism remained surprisingly efficient. Running with newspapers in the streets is as strenuous an occupation as any which a boy is likely to undertake. Yet during this time our patient was practically free from symptoms. Even at the end, when we saw him during the last few weeks of his life, though he was extremely dyspnoeic on the slightest exertion, and though the left auricle was enormously dilated, there was no oedema and only very slight enlargement of the liver.

At autopsy both ventricles were found to be greatly hypertrophied. It seems probable that the hypertrophy had developed gradually during the ten years which followed the initial illness. Its very occurrence implies that the heart muscle during this period must have been nearly able to meet its extensive liabilities. If a greatly increased demand be made suddenly upon a heart which has not undergone careful and gradual 'training', it leads to dilatation with failure and not to hypertrophy. The ability to hypertrophy suggests that between the ages of 10 and 20 the work which the heart was called upon to perform was never greatly in excess of its capacity. It had, so to speak, a continual debit balance; but, thanks to the fact that the hypertrophy was able almost to keep pace with the increased demands of physical exertion, the debit balance did not increase to an embarrassing extent. Subsequently, however, some additional factor, probably the onset of fibrillation, made its appearance, and the overdraft was converted into bankruptcy.

The auricular dilatation can have played but a minor part in the clinical picture. So far as the functional efficiency of the heart was concerned it was really a side-issue, though it caused collapse of part of the right lung, and thereby no doubt supplemented to some extent the other factors already limiting the exercise tolerance.

In Cowan's case the history of continuous shortness of breath on exertion suffices to date the onset of the cardiac trouble to the first attack of rheumatic fever at the age of 12. The patient was known to have had mitral stenosis and auricular fibrillation from the age of 27. Yet in spite of four attacks of rheumatic fever, in addition to other illnesses, the heart did not finally break down until the age of 38, eight years after the last of six confinements, all of which were carried to a successful conclusion.

The extreme irregularity of the pulse described in Case IX suggests that fibrillation was already established at the time of the patient's first admission to

hospital, twelve years before her death. Possibly it may have been present for eighteen years, for palpitation had been troublesome for six years before she came under observation. In Case XI there was an embolic hemiplegia eight years before death, and auricular fibrillation was known to have been present for at least four years.

In all these cases the capacity of the heart to meet its liabilities is remarkable. We believe it is to be explained by the fact that the brunt of the lesion was borne by that relatively unimportant chamber, the auricle. When the fibrotic lesion is strictly confined to the auricle, and spares the more important ventricle, it may lead to great auricular dilatation, and at the same time interfere but little with the efficiency of the circulatory mechanism. Thus life may be prolonged for many years, during which time the damaged auricle is subject to conditions very different from those in the average cardiac patient, whose physical capacity is strictly limited by the ventricles having borne an equal share in the rheumatic process.

It is not uncommon to meet with patients in whom the physical signs of a gross structural lesion in the heart are associated with surprisingly little disturbance of function, or what at one time used to be spoken of as 'advanced valvular disease with good compensation'. To assess with accuracy the capacity of such hearts to meet the demands likely to be made upon them, and to foretell the weight which will eventually upset the balance on the side of failure, is often extremely difficult. If we are right in believing that the localized nature of the lesion plays an important part in the evolution of the cases described in this paper, the study of aneurysmal dilatation of the auricle may help to throw some light on the mechanism of cardiac dilatation in general, and lead to a clearer understanding of the part which cardiac dilatation plays in producing impairment of the efficiency of the circulatory mechanism.

Radioscopic Appearances.

With the patient facing the screen, the right border of the heart shadow is generally formed in its entirety by the right auricle, though occasionally in normal subjects, and frequently under pathological conditions, the lower part of this border is formed by the right ventricle (31). The shadow of the right ventricle can be distinguished from that of the auricle by the fact that pulsation in the former case coincides with, while in the latter it precedes that of the left ventricle. But the somewhat surprising fact that the *right* border of the heart shadow may occasionally be formed by the *left* auricle is demonstrated by the cases described in this paper. In extreme dilatation of the left auricle the physical signs considered in conjunction with the radioscopic appearances suffice to clinch the diagnosis; but when the dilatation is less pronounced, the diagnosis must depend largely upon the radiological appearances, and the distinction between right and left auricular dilatation may present some difficulty.

Schott (28) reports six cases which have recently come under his observation

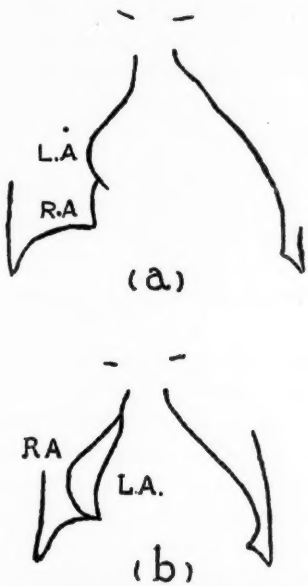

FIG. 7. Orthodiagrams from two of Schott's cases.
R. A. = outline of right auricle. L. A. = outline of left auricle.
(*a*) Moderate dilatation; left auricle forming upper part of right border of heart shadow.
(*b*) Extreme dilatation; left auricle forming entire right border of heart shadow.

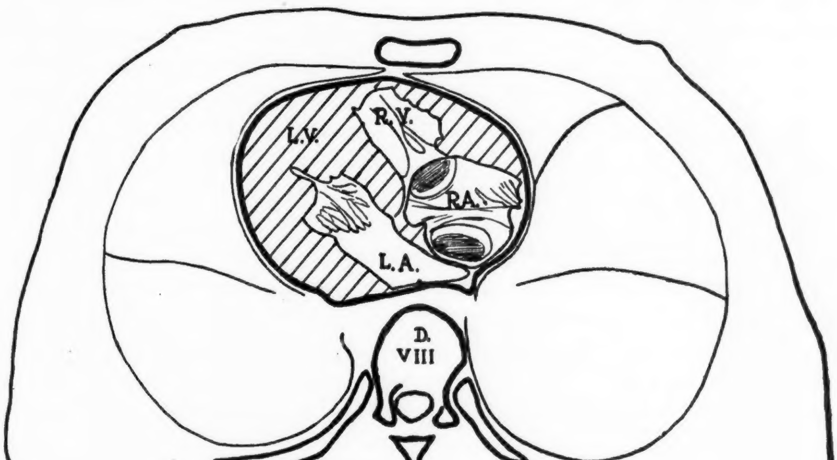

FIG. 8. Transverse section through the chest at the level of the body of the 8th dorsal vertebra (tracing modified from Braune), to illustrate relative anatomical positions of right and left auricles.
R. V. = cavity of right ventricle. R. A. = cavity of right auricle.
L. V. = left ventricle. L. A. = cavity of left auricle.
D. VIII = body at 8th dorsal vertebra.

at the first University Medical Clinic in Vienna, in which the right border of the heart shadow appeared to be formed wholly or partly by the left auricle. In the three cases which showed the greatest enlargement, the outline (Fig. 7, *b*) of the right auricle could be recognized as a more dense shadow, the outer margin of which lay well inside (i. e. to the left of) the right border of the heart. In the remaining cases the right border of the heart shadow was formed by two convex curves, the one above the other, the upper being the outline of the left and the lower that of the right auricle (Fig. 7, *a*). In addition to the extension of the heart shadow to the right in these cases, examination with the patient in the oblique position showed a dome-shaped projection extending backwards towards the vertebral column.

In two of Schott's cases the X-ray diagnosis was confirmed at autopsy, while in the remainder it was based on the gradual change in contour of the heart observed over a considerable number of years. In two [4] only of Schott's cases was the degree of enlargement comparable to that in the cases which form the basis of this paper, but the slighter degrees of dilatation which he has observed suggest that, as one would expect, all transitional stages do occur, though the slighter degrees of enlargement often escape recognition.

The most favourable position for radiological examination of the right auricle is the antero-posterior (i. e. with the patient facing the screen). Dilatation of the left auricle, on the other hand, owing to its proximity to the vertebral column (Fig. 8), can be most easily recognized in one of the oblique positions, either the right posterior (i. e. with the patient facing towards 2 o'clock) or the left anterior (i. e. facing towards 8 o'clock). In dilatation of the left auricle enlargement tends to take place in a backward direction towards the vertebral column. The shadow of the enlarged auricle fills the upper part of the posterior mediastinum, which in normal subjects, on screening in the oblique position, appears as a clear space separating the heart from the vertebral column. By comparing the appearances in the oblique and in the antero-posterior positions dilatation of the left and right auricles can be distinguished radiologically.

The backward extension of the auricle in the retrocardiac space is of interest in connexion with the auscultatory phenomena observed in these cases. Turrettini (30) has suggested that the anatomical relations, when the heart comes in direct contact with the vertebral column, may account for the extensive area over which the systolic murmur is clearly audible in certain cases of mitral regurgitation, the sound vibrations being transmitted directly to the bony framework of the thorax.

Pathogeny of aneurysmal dilatation. In most of the cases collected in this paper, fibrosis of the auricular wall appears to have been due to an ischaemic necrosis associated with a rheumatic infection, carried by the blood-stream. Occasionally, however, it may result from direct invasion of the heart wall by some morbid process spreading from an adjacent organ. In Case III, for example, a tuberculous focus in the lung, and in Case XVI a gumma, was responsible or at

[4] Cases XIII and XVII described above.

any rate partly responsible for the cardiac lesion. But whatever be the nature of the infective process, the resulting mechanical disability is the same, for it causes a fibrosis with consequent weakening of the heart wall which predisposes to dilatation.

Summary and Conclusions.

1. Two cases of old-standing rheumatic carditis with extreme dilatation of the left auricle are described.

2. A brief summary is given of other similar cases, some of which have already been reported in the literature.

3. The mechanism of production of this peculiar lesion is discussed. The evidence suggests that the condition cannot be accounted for either by pericardial adhesions or by any associated lesion of the mitral valve, but that it is due to a chronic ischaemic fibrosis of the auricular wall, and is therefore analogous to aneurysm of the ventricle.

4. The exercise tolerance in many cases remains surprisingly good considering the advanced nature of the structural lesion. It is suggested that this can be explained by the fact that the brunt of the damage is borne by the auricle, whereas the muscle of the ventricle remains relatively healthy, and indeed often exhibits considerable hypertrophy.

5. The radiological diagnosis of the condition is discussed.

We wish to thank Professor J. Shaw Dunn for his helpful criticism of the pathological aspect of this paper.

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DESCRIPTION OF FIGURES.

PLATE 10, FIG. 1. Radiogram of chest, Case I, with patient facing the screen. The shadow filling the right side of the chest is due to the left auricle.

PLATE 11, FIG. 2. Photograph of heart, Case I.

PLATE 12, FIG. 4. Section of hypertrophied portion of wall of left auricle, × 50, Mallory's stain. Blue = fibrous tissue, bright red = blood corpuscles, dull red = muscle.

Ep = epicardium. *My* = hypertrophied myocardium.
En = thickened endocardium.

FIG. 5. Section of fibrosed (aneurysmal) portion of wall of left auricle, × 50, Mallory's stain.

Pe = adherent pericardium. *Ep* = epicardium.
My = fibrosed myocardium. *En* = thickened endocardium.

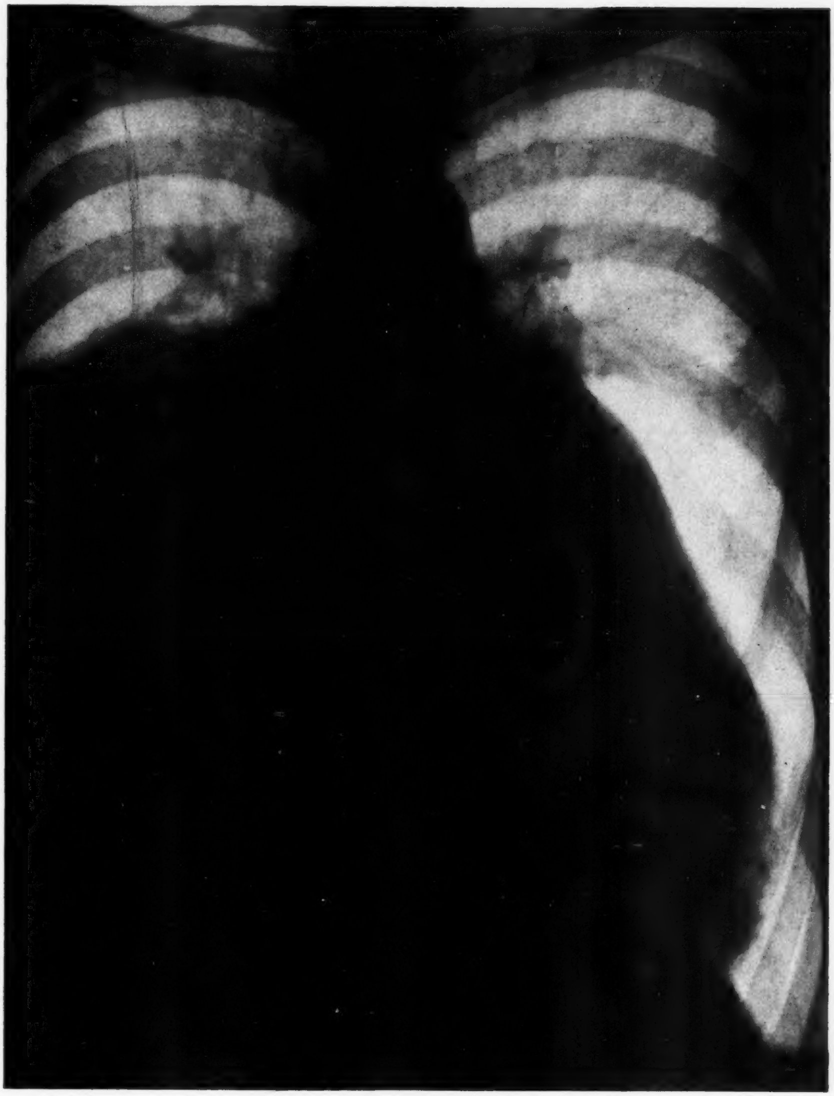

FIG. 1

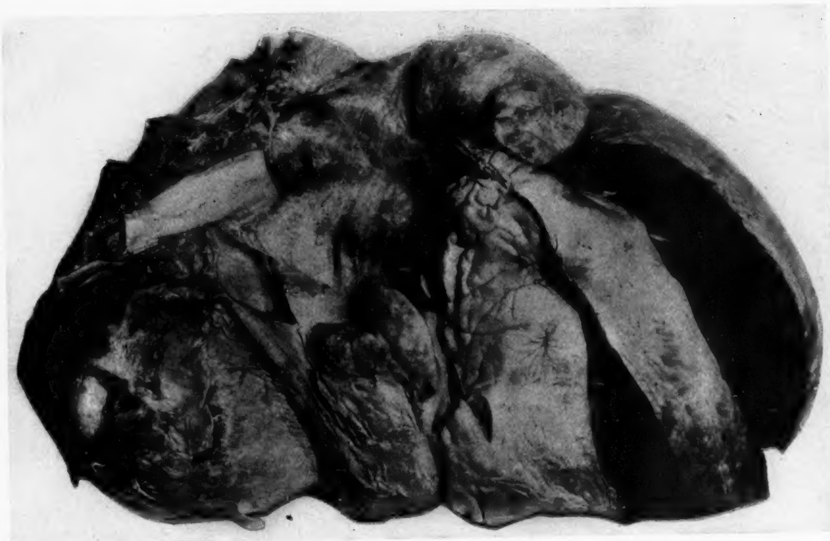

Fig. 2

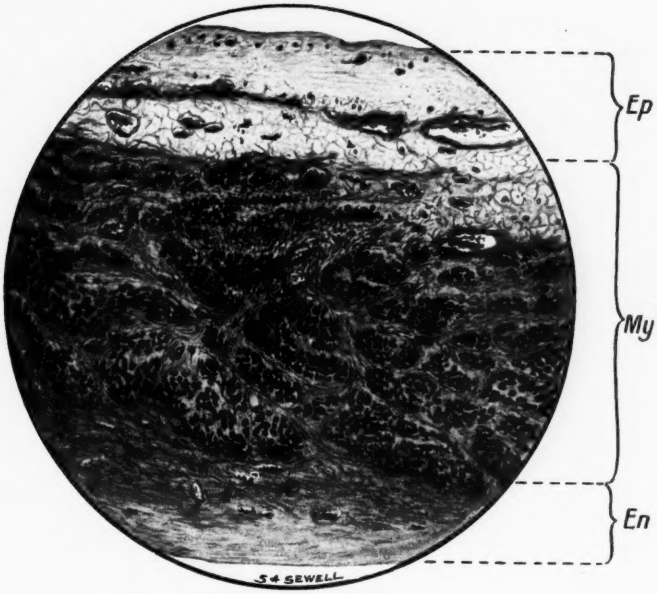

Fig. 4.

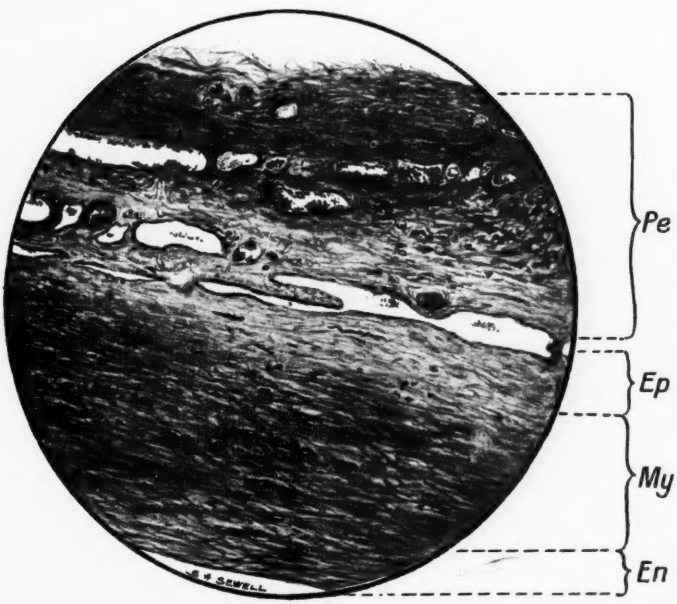

Fig. 5.

DOES INSULIN IMPROVE CARBOHYDRATE TOLERANCE IN DIABETES?[1]

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The Altered Outlook in Diabetic Therapy.

It is hardly necessary to dilate upon the value of insulin in the treatment of diabetes mellitus. The physical state and mental attitude of the diabetic, uncontrolled by diet alone, speak for themselves. Death from uncomplicated diabetes is and should now be an uncommon occurrence. Diabetics can now be exposed to major surgical procedures of long duration, using anaesthetics of different kinds, and the mortality rate is relatively low. With proper preoperative and post-operative medical care, death due to diabetic coma, and brought on by anaesthesia, is, and should be, a rare occurrence. Insulin has, however, been employed in a sufficiently large number of cases and for a sufficient length of time to enable us to answer a question just as important as, if not of greater importance than, how long the diabetic can be kept alive. Can insulin treatment result in a cure? If not, can it result in a partial cure? And if not, can it at least improve carbohydrate tolerance?

There are no records available, clinical or experimental, which demonstrate a cure. As far as I could ascertain from the literature, there is only one record of an investigation into the question as to whether insulin treatment can result in a partial cure. Harrison (1), at King's College Hospital, London, has been unable to demonstrate a partial remission of the disease in a careful study of five selected cases with observations lasting eleven to eighteen months. All of the five patients needed as much or slightly more insulin at the end of the observation periods. Such fluctuations in dosage of insulin as occurred were attributed to difficulties in balancing the dose of insulin accurately against the diet, variations in the potency of the insulin, and alterations in metabolic activity of the tissues.

Can Insulin improve Tolerance for Carbohydrates?

This question is, obviously, just as important as that just discussed. There is no sharp line of demarcation between improvement of carbohydrate tolerance and cure. It is only a matter of degree. If improvement of carbohydrate

[1] Received July 7, 1927.

tolerance could be definitely demonstrated this would be sufficient to encourage the belief that partial or real cure may be a function of time. An investigation along these lines was made at the Montreal General Hospital, and it is the purpose of this paper to record the results.

Differing from the unanimity of opinions that insulin does not effect cures, there appear to be differences of opinion as to its ability to improve carbohydrate tolerance. One's experience with diabetes need not be very large before one notices instances which do suggest improvement of tolerance. Diabetics are known to require insulin on admission to the hospital, and before discharge, or some time after, are able to reduce the amounts taken or do without it entirely. Also there appears to be anatomical evidence in favour of improvement in tolerance. Boyd and Robinson (2) have reported a case of a child killed in an accident shortly after having been discharged from the hospital, and having improved markedly following insulin treatment. The clinical response to insulin, associated with the anatomical changes found, was strongly suggestive of regeneration of pancreatic tissue. Whether, however, anatomical integrity necessarily parallels functional efficiency is an unsettled problem. We know that such parallelism is not always found in the case of the kidneys.

Clinical Varieties.

The greatest difficulties one encounters in interpreting results of an investigation of the kind we have attempted are the possible variations of the disease itself, and the numerous factors which may influence the courses of the different types. One may here repeat an often-quoted remark. Sir Rose Bradford put it very well when he stated that 'diabetes is not an entity, but a clinical label attached to a number of different conditions with varied origin, different morbid anatomy, and liable to follow different courses'. The truth of this statement becomes only too evident in the course of the treatment of a series of such patients. For example, there is the acute diabetic. This individual, known to have no glycosuria, very shortly after some illness, probably of a very mild nature, rapidly develops glycosuria and acidosis and progresses to the stage of coma. With relatively small doses of insulin he is brought out of coma, and in a very short time requires no insulin and takes a fair amount of carbohydrate. In our last case of this type, this period of time was three weeks. Such patients observed over a period of two or three years do not appear to have made any downward progress. One case I have in mind is now able to take about 250 grm. of carbohydrate a day. As is obvious to any one familiar with food values, this represents a very liberal carbohydrate diet.

There is the 'juvenile diabetic', who may run a rather acute course, rapidly develop severe acidosis, and progress to a stage of coma, and, as in the acute diabetes of adults just mentioned, following insulin treatment, may be brought out of coma and eventually require little or no insulin while on fairly liberal diet. One striking example of this type of case was a child of twelve years of age. Eight

days following her recovery from coma, the urine was sugar free, the blood sugar was normal, and it was possible to discontinue the use of insulin.

Then there is the very mild diabetic whose tolerance is suddenly lowered by an infection, and progresses rapidly to the stage of severe acidosis and coma. One such patient developed pneumonia, and, in spite of taking sixty units of insulin a day, could barely be kept free of acidosis. Hyperglycaemia and glycosuria were very difficult to control. Following recovery from the pneumonia it was possible to discontinue the use of insulin, and the patient now takes sufficient food to maintain his normal body weight, the urine sugar free, and the blood sugar normal.

In view of the very limited knowledge we have of the peculiar metabolism of these three types of the disease just mentioned, and in view of such rapid fluctuations in carbohydrate tolerance as they may show, it is obvious that such patients are not suitable for an investigation of the kind which we have attempted. We are therefore left with the other form of the disease, which, fortunately for this purpose, represents by far the great majority of patients, namely, the chronic and (in the absence of treatment) progressive diabetic. The course of the majority of these patients is very clear. At first the glycosuria which develops is transient, and may be absent for intervals of weeks. As the carbohydrate tolerance is lowered, the glycosuria appears more frequently, and then becomes postprandial, appearing regularly a few hours after meals. As the disease progresses, the glycosuria becomes persistent, being found throughout the day. With further lowering of carbohydrate tolerance acetone bodies make their appearance, and in time, in the absence of treatment, these patients, slowly but surely, progress to the stage of coma.

Because of the slow progress and the relative ease with which it is possible to determine the carbohydrate tolerance of these individuals, they make ideal subjects for this study. The problem is, however, not simple. Though we may be dealing with a condition which runs a fairly slow and steady course, and the metabolism of which is fairly understood, there are many variables to consider.

In view of previous observations on the influence of infection, diabetics having foci of infection, though belonging to this group, cannot be included in such a study. From this group must also be excluded those subjects with a history of gall-bladder disease, i.e. those patients known to have diabetes definitely pancreatic in origin.

Having selected the subjects, a most difficult factor to exclude is the influence of fasting. The value of starvation in improving carbohydrate tolerance is well known. Though one can avoid fasting when calculating diets for subjects at rest in bed, by adding to the basal diets the equivalent of about 10 per cent. of the total basal heat production, it is necessary to make additional allowances for the amount, frequency, and regularity of exercise when the subjects are out of bed. It is obvious that with an individual not at rest in bed, and on a diet of constant composition, the degree of fasting will depend upon the degree of muscular activity.

Patients whose diets are constructed on the basis of calculated, rather than experimentally determined, caloric requirement may actually be fasting, though the degree of under-nutrition may be mild. Continued, however, over a long period of time such diets will influence the course of the diabetes, in that they will tend to improve carbohydrate tolerances regardless of the insulin administered.

In addition to this there is the difficulty of determining exactly how much food patients are receiving. In spite of accurately weighing food we have previously shown (3) that patients may be receiving as much as 25 per cent. either more or less of carbohydrate than is intended unless the diets consist of dairy products only, milk, cream, butter, &c., of which a large number of analyses have been made and the percentage compositions are fairly accurately known; the composition of other foods vary widely.[2]

Then we have the influence of acidosis. Many patients on admission to the hospital have this complication. An increased metabolic rate generally accompanies it. Diets constructed on calculated rather than experimentally determined caloric requirements may therefore fall short of the needs of the individual, at least temporarily, and fasting may unintentionally play its part.

Insulin improves the general attitude of the individual and gives him a brighter outlook on life in general. Muscular tone is increased. This increases metabolism, and, providing the diet remains the same, will obviously result in some degree of fasting.

Criteria of Altered Tolerance.

It is obvious from the foregoing observations that such a study as this is rather complicated. It is, at times, possible, however, by the application of modern statistical methods to draw approximately accurate conclusions from what appears to be a very complicated or even insoluble problem. Such methods were adopted for this investigation.

[2] This fact is recognized by the U.S. Department of Agriculture in publishing the Atwater-Bryant food tables, Bulletin No. 28, but apparently not generally by those employing the same tables in constructing diets. In the introductory remarks to this publication it is stated: 'In the present publication it is the intention to give the maximum, minimum, and average of all available analyses of American food products up to January 1, 1899, with the exception of milk, butter, and other dairy products, and sugars. The number of analyses of such products is so great, and the literature of the subject so large, that a compilation of the results might appropriately form the subject of a special publication.' And later: 'As a necessary basis of this tabulation the individual analyses have been collated in detail. In many cases the number of analyses of a single product was considerable, and it is believed that the averages which are given in the tables may be advantageously used in computing the composition of foods used in dietary studies, &c.' It will thus be noted that only in the case of dairy products are the average values recommended. This recommendation is obviously based upon one of the theorems of statistics, namely, 'the arithmetical mean of a large series of observed values is the most probable value of the quantity measured'. Where the number of analyses is small, meats, vegetables, &c., it is necessary to know more than the average compositions. In spite of these facts it is generally assumed that the average values given in these tables are the most probable for *all* foods, and they are accepted as face value in calculating diets.

Our object was to attempt to demonstrate whether insulin does or does not improve carbohydrate tolerance. Proof of such improvement may be regarded as having been demonstrated by either one of the following results:

(*a*) The patient, after having been proved to require insulin and having had it for a period of time, can increase the total caloric value and carbohydrate content of the diet, and at the same time not increase the dose of insulin; or, (*b*) The patient, after having been proved to require insulin as having had it for a period of time, can, without altering the carbohydrate or caloric content of the diet, reduce the amount of insulin taken.

If, when either the dose of insulin has been decreased and the same diet maintained, or the diet has been increased on the same dosage of insulin, the urine fails to remain sugar free and the blood sugar normal, this is proof that no increase of tolerance has taken place.

Proof of requiring insulin is the fact that the individual cannot maintain his body weight, and at the same time keep the blood sugar normal and the urine sugar free on diet alone.

In either case no other factors, such as fasting, must operate, which, by themselves, would tend to improve carbohydrate tolerance.

The Influence of Different Diets.

The first problem with which we were confronted was to eliminate the influence of the diets given to patients receiving insulin, since diets resulting in starvation tend to improve carbohydrate tolerance regardless of insulin. In our clinic, as most likely in all others, the general plans followed in the dietetic management of the patients have been those involving either 'ladder' or 'basal' diets. For insulin patients we at first confined ourselves to basal diets as outlined by the Toronto workers. Since such basal diets in the early period of management do not allow for energy expended in the usual muscular activities of bed patients, nor for that due to the specific dynamic action of food, it is obvious that, though they are not rigid starvation diets, they may result, over a period of time, in some degree of fasting.

The 'ladder' diet which we generally employ is shown in Table I. It will be noted that after three 'green days' the diet is gradually increased to basal caloric requirements. During the period in which the amounts of food are being increased and the total amounts are still below the basal requirements, it is obvious that the degree of fasting would be much greater than that obtained with the 'basal' type of diet. With the latter the degree of fasting is represented only by the deficiency of calories necessary to meet the energy expenditure as a result of muscular activity and the specific dynamic action of food.

For the purpose of determining quantitatively the difference between the two diets, the records of 500 non-insulin diabetics were investigated—250 represented 'ladder' diets, and 250 represented 'basal' diets. The average time

taken for the patients of each group to become sugar free was calculated. The data necessary for the calculations are shown in Table II. The first column represents the days necessary to render the urines sugar free. The second and

TABLE I.

Ladder Diet.

Day.	Carbohydrate.	Fat.	Protein.	Calories. per Day.	Calories. since First Day of Treatment.
	Grm.	Grm.	Grm.		
1	15	20	25	340	340
2	15	20	25	340	680
3	15	20	25	340	1020
4	20	50	30	650	1670
5	25	75	35	915	2585
6	30	100	40	1180	3765
7	35	125	45	1445	5210
8	40	150	50	1710	6920
9	45	150	50	1730	8650
10	50	150	50	1750	10400

TABLE II.

Showing the Number of Days necessary to render Urine Sugar free by means of 'Ladder' and 'Basal' Diets.

Number of Days.	Incidence. Ladder Diet.	Incidence. Basal Diet.	Number of Days.	Incidence. Ladder Diet.	Incidence. Basal Diet.
1	16	1	12	3	16
2	46	4	13	5	4
3	62	5	14	2	11
4	34	3	15	4	9
5	17	8	16	2	6
6	10	16	17	0	12
7	12	7	18	1	5
8	13	18	19	1	1
9	16	35	20	—	3
10	4	56	21	—	1
11	2	29			

third columns represent the incidences of such periods with the 'ladder' and 'basal' diets respectively. For each group were then calculated, in order, the standard deviation and the probable error of the mean.[3] The difference between

[3] Standard deviation $= \sqrt{\frac{\Sigma d^2}{N}}$, where Σd^2 is the sum of the squares of the residual errors and N is the number of observations.

Probable error of the mean $= 0{\cdot}67449 \frac{\sigma}{\sqrt{N}}$, where σ is the standard deviation.

Probable error of the difference $= \sqrt{(P)^2 + (P_1)^2}$, where P and P_1 are the probable errors of the means.

Ratio of difference between means to the probable error of the difference

$$= \frac{M_1 - M}{\sqrt{(P)^2 + (P_1)^2}}.$$

the means of both groups and the probable error of the difference were then obtained. From the ratio of the difference to the probable error of the difference was determined whether the differences noted between the two diets were due to chance or actually the result of diet. Thus:

Number of observations of 'ladder' diet	250 (N)
Number of observations of 'basal' diet	250 (N^1)
Average number of days necessary to render urine sugar free with 'ladder' diet	4·9 (M)
Average number of days necessary to render urine sugar free with 'basal' diet	10·3 (M^1)
Standard deviation of 'ladder' diet	3·6 (σ)
Standard deviation of 'basal' diet	3·7 (σ_1)
Probable error of M	0·15 (p)
Probable error of M^1	0·16 (p^1)
Difference between means ($M^1 - M$)	5·4
Probable error of the difference	0·22

$$\frac{\text{Difference}}{\text{Probable error of difference}} = 24.$$

It is obvious that in this group of subjects the individuals, though selected by excluding the three types previously discussed, will still represent the disease in different degrees of severity. This is a complicating variable. They are, however, known not to be very mild, and also known not to require insulin. They belong to what are known in this hospital as Types 3 and 4, previously described (4). That is, they have persistent glycosuria with and without acetonuria. There is no reason, however, on the basis of probabilities, for a larger number, representing any particular severity, being found in one group more than the other. If a difference should be found between the results of the two diets, statistical treatment of the average values by the above method should demonstrate the part that chance may have played in having produced it.

It will be observed that the average period necessary to render sugar free the urines of patients on the 'ladder' diet was 4·9 days, whereas on the 'basal' diet it was 10·3 days. Now was this difference of five days between these averages caused by the different diets or the result of chance? From the statistical data given it is seen that the difference between these two averages, namely, 5·4, was twenty-four times the probable error of the difference (i. e. 5·4 ÷ 0·22). In other words, it may be stated, the chances of the difference being fortuitous or the result of chance were so slight that it is practically certain that the difference is not the result of random sampling.

Can this difference be attributed to the effects of starvation only? The average basal food requirement of an individual in this group was 1,463 calories per twenty-four hours. If we allow an additional 10 per cent. of this for the muscular activity of bed patients the average daily requirement is about 1,600 calories. It is known that such non-insulin patients become sugar free in an average of three days of complete starvation. They therefore become sugar free following a deficit of about 4,800 calories. In Table III are shown the daily and total deficits of patients on the 'ladder' diet. In calculating total require-

ment of individuals taking food an additional 10 per cent. must be added to the basal requirement for the specific dynamic action of food. The total daily requirement is therefore 1,755 calories. It will be observed that a deficit necessary to render the urine sugar free, that is, a deficit of 5,265 calories, occurs about the fourth day of treatment. The actual period observed as noted above was about five days.

TABLE III.

Showing Daily and Total Caloric Deficits of 'Ladder' Diet.

	Food.				Caloric Deficit.	
Day.	C. Grm.	F. Grm.	P. Grm.	Calories.	Daily. Calories.	Total. Calories.
1	15	20	25	340	1415	1415
2	15	20	25	340	1415	2830
3	15	20	25	340	1415	4245
4	20	50	30	650	1105	5350
5	25	75	35	915	840	6190
6	30	100	40	1180	575	6765
7	35	125	45	1445	310	7075
8	40	150	50	1710	45	7120
9	45	150	50	1730	25	7145
10	50	150	50	1750	5	7150

That caloric deficiency is probably not the only influencing factor is suggested from the data of the basal diets. Assuming an average requirement of 1,755 calories per day, the patients on the 'basal' diets were fasting to the extent of about 300 calories per day. Since an average deficit of 4,800 calories is necessary to render urine sugar free of such patients, it should have taken about sixteen days to accomplish this. The actual time taken was ten days.

The object of the above investigation was to determine, quantitatively, the difference between the effects of diets from the point of view of their ability to render urine sugar free. It will be noted that the 'ladder' diet was more effective, but the important fact is that the 'basal' diet had also the same effect but required a longer period of time. *The possible influence of such diets improving carbohydrate tolerance must therefore be considered in the interpretation of possible reduction in insulin dosage.*

Results of the Inquiry.

In our clinic there were sixty-nine cases observed in which, after varying periods of time, it was possible to reduce the doses of insulin given. A statistical study was made in order to determine if possible the cause or causes of these reductions. Some of these patients were kept in bed, and others allowed to walk about. Some had acidosis. An attempt was made to determine the influence of these factors. The subjects were therefore divided into the following groups and sub-groups:

Group 1. (*a*) In bed; (*b*) Walking about.
Group 2. (*a*) With acidosis; (*b*) No acidosis.
Group 3. (*a*) No acidosis and walking about; (*b*) No acidosis and in bed.
Group 4. (*a*) Acidosis and walking about; (*b*) Acidosis and in bed.

For each group and sub-group were calculated the average number of days taken before the doses of insulin could be reduced from the time the diets and doses of insulin were fairly well regulated. The differences between the average values of the sub-groups of each group were then treated statistically, and the probable errors determined. By means of this procedure it was possible somewhat to clarify the picture. The combined data are shown in Table IV.

TABLE IV.

Showing Influence of Increased Metabolism on improving Carbohydrate Tolerance.

Group.	Number of Cases (N).	Arithmetical Mean Days (M) noted before Insulin could be reduced.	Standard Deviation (σ).	Probable error of $M = 0.67449 \frac{\sigma}{\sqrt{N}}$.	Probable error of difference between Means.	$\frac{\text{Difference between Means}}{\text{Probable error of Difference}}$
1. (*a*) Walking	30	19·0	7·8	0·95	1·77	10·9
(*b*) In bed	39	38·4	14·0	1·50		
2. (*a*) With acidosis	40	24·1	11·1	1·17	2·30	6·0
(*b*) No acidosis	29	37·9	16·0	1·98		
3. (*a*) No acidosis. Walking	11	23·0	6·5	1·31	2·39	10·1
(*b*) " " In bed	18	47·0	12·8	2·01		
4. (*a*) Acidosis. Walking	19	16·6	7·2	1·10	1·86	7·7
(*b*) " In bed	21	31·0	10·2	1·50		

Here again, as with those cases not requiring insulin, the disease was probably represented by various degrees of severity. The argument, however, holds here also that, on the basis of probabilities, there is no reason for a larger number representing any particular severity selecting one group more than another.

It will be noted from the average values in the table that, in all the groups, walking and acidosis appear to be factors influencing the reduction of the amounts of insulin. Since walking and acidosis increase the metabolism of the individual and since all these subjects were on 'basal' diets they were obviously fasting. The probabilities of the differences in the averages found being the result of chance are shown in the last column of the table. These demonstrate that the differences found were not the result of random sampling, but actually due to fasting. For example, the lowest ratio of the difference between the means to the probable error of the difference was 6·0 (Group 2). With this

value it can readily be shown that the odds against the occurrence of a deviation as great or greater than 6, as a result of random sampling, are over 1,000 to 1 (actually 1,341 to 1).

Summary.

An attempt was made to determine whether insulin does or does not improve carbohydrate tolerance. In view of the number of variables entering into the problem the method of approach was statistical.

The general method employed to determine the influence of any particular variable was to divide the subjects into two groups, in one of which the variable studied was excluded as much as possible. The average result in each group was calculated and the difference between the averages noted.

The probable errors of the averages were then calculated, and conclusions were drawn from the ratios of the differences between the averages of each group to the probable errors of the differences.

The three variables observed so far were diet, exercise, and acidosis.

In view of the fact that insulin patients were given during the early period of treatment diets calculated on the basis of caloric requirement in the basal metabolic state, the possible influence of such diets as carbohydrate tolerance was investigated. For this purpose the effects of 'basal' diets were firstly compared with those of the 'ladder' or starvation type in rendering the urines sugar free. It was found that the quantitative effects of 'basal' diets continued over a period of time could be measured approximately. The time taken to render urines sugar free on such diets was greatly a function of deficiencies in caloric values, i.e. a function of the degree of fasting. Since fasting tends to improve carbohydrate tolerance the effects of such basal diets when given in combination with insulin must be considered in the interpretations of possible reductions in the amounts of the latter.

A series of diabetics requiring insulin, but who were able in time to reduce the amounts taken, were then observed. The subjects were grouped in order to study the influences of some factors, the presence of which would tend to result in fasting and improve carbohydrate tolerance regardless of insulin. The effects of muscular activity and increased metabolism accompanying acidosis, when not allowed for in the calculation of diets, were observed. Wherever these factors were found to operate, it was possible to reduce the amount of insulin taken.

Though it has been demonstrated statistically that 'basal' diets, 'exercise', or 'increased metabolism' in general could account largely for reductions in the amounts of insulin taken, these do not appear to be the only influencing factors. The individuals in the control groups, in which exercise and acidosis were excluded, were also able to reduce the amounts of insulin taken, but after a longer period of time. In explaining reductions in dosage of insulin after much longer periods (years) the influence of time upon recuperation of pancreatic function is to be considered. This is mentioned in view of the recent observations of Root and Warren (5) made in Joslin's clinic.

Though the investigation is incomplete, the findings of the effects of exercise, fasting, muscular activities, &c., appear to be of sufficient clinical importance to warrant publication. They emphasize further, if further emphasis is necessary, the great underlying principle to be followed in the management of the diabetic, namely, under-nutrition. It is most tempting at times to allow the diabetic more insulin and more liberal quantities of food. To do so in view of our present knowledge depends upon whether we are seeking immediate results only or those of a more lasting character. In connexion with this is an observation made in a recent editorial (6) by one responsible for insulin: 'When depancreatinized dogs treated with insulin are made fat, by feeding them with excess of carbohydrate, they exhibit much more acute symptoms of diabetes when insulin is withdrawn than are observed under the same circumstances in the case of thin dogs. The hyperglycaemia, ketonemia, and glycosuria are all more intense, but, most striking of all, the general symptoms are extremely acute and a fat animal seldom lives for more than four days after discontinuing the insulin, whereas a thin one may live several weeks.'

In our clinic, at the time this paper was being written, there were over 1,200 diabetics. The average age of this group was 47 years. At this age the expectation of life is about 24 years. That is a long way to go, and our object should be to reach that goal if possible. Until clinical or experimental data are available, definitely demonstrating that insulin does improve carbohydrate tolerance, treatment, at least in my opinion, should aim in that direction which tends to do so, namely, construction of diets not only low in carbohydrate but also in caloric content, whether the individual does or does not require insulin.

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GOITRE IN THE ENGLISH SCHOOL CHILD[1]

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Introduction.

THE main purpose of this paper is to make a critical analysis of the results of the survey carried out by the school medical officers at the request of the Board of Education in 1924, with the object of ascertaining the geographical incidence in England and Wales of enlargement of the thyroid gland in boys and girls about the age of 12 years. The results of this survey have not hitherto been published in detail.[2] A partial analysis of some of the returns has been made by J. M. H. Campbell in a paper in the *Journal of Hygiene*,[3] but without attempting to estimate the effect of the personal equation. An examination of the original records which were given to me by the Medical Department of the Board of Education showed the personal factor to be of such importance that no sound conclusions could be drawn as to geographical incidence of thyroid enlargement and its relation to physiographical and geological features until the magnitude of the personal variation had been assessed by direct observations, and an attempt made to calculate the probable errors in the returns arising from it. It has been necessary from considerations of space to give only a condensed account in the earlier sections of this paper of the statistical process by which the expressions for the probable errors in Table IX were arrived at, and some of the intervening steps must be taken on trust.

It may be well here at the outset to show by an example how serious is the effect of the personal equation in this survey in order to justify the somewhat tedious processes in the first part of the paper. Let us suppose that two neighbouring county areas, each with four school medical officers, returned rates of thyroid enlargement amongst girls aged 12, amounting respectively to 10 per cent. and 25 per cent.; it would be at once concluded that goitre was much more prevalent in the latter than the former, but an application of the formulae arrived at in Table IX shows that the apparent difference of 15 per cent. is subject to a probable error exceeding 5 per cent., which means that such a difference could

[1] Received August 31, 1927.

[2] The crude returns from the county areas and county boroughs have been tabulated in a recent paper by the author for the purpose of correlating them as they stand with the distribution of other diseases, but analysis of the returns from the geographical standpoint was deferred to the present paper. See Reference No. 1.

[3] See Reference No. 2.

quite possibly arise by the operations of pure chance in the location of the personal equations of the eight medical officers concerned,[4] or in statistical language the difference is not significant.[5] This example should suffice to show that comparative surveys of this kind, however conscientiously carried out, even on hundreds of thousands of individuals, may be only misleading, unless subjected to careful analysis by statistical methods.

I must here express my thanks to the Medical Department of the Board of Education, and to the medical officers mentioned in this paper, for their cordial assistance, and also to my colleague Miss M. N. Karn for her help in computation, and to Miss I. McLearn for drawing the diagrams and map.

The School Medical Officers' Survey of 1924.

Being impressed with the importance of attempting to ascertain the nature of the geographical distribution of goitre and thyroid enlargement amongst school children in England and Wales, Sir George Newman circulated in March, 1924, a request to all school medical officers to make if possible during the year a return of the numbers of boys and girls aged 12 'in whom the thyroid is sufficiently enlarged for the increase in the size of the neck to be noticed on casual inspection without measurement or palpation'.

It is unnecessary to go into the reasons which led to the use of this form of definition. In the absence of any standardized method of measuring the gland, the choice of a satisfactory definition of what they were to consider constituted 'enlargement', for use by some hundreds of different medical men, was not an easy problem, and it is difficult to see how any better definition could have been devised for such a purpose. One can only regret that it was not possible to detail a single medical officer to spend six months in making a sampling survey of the whole country, for a rough calculation shows that the probable errors of the resulting rates due to sampling would have been only about one quarter of the magnitude of the probable errors due to the personal equation as calculated in the following pages, notwithstanding that only one-fifth of the number of children would have been examined by the sampling method.

Some six hundred medical officers took part in the survey and a large personal equation was inevitable. The total children aged 12 examined were 375,022. London, the county areas of Anglesey, Cambridge, Cumberland, Montgomery, Staffordshire, Suffolk, and Westmorland, and about fifty independent towns and urban districts were not able to participate, and the aggregate population of these blank areas, excluding London, was about 3,200,000 out of a total population of 34,150,000. The total children of the 12-year age group on the registers of the

[4] If the rate of thyroid enlargement were everywhere uniform and medical officers with their varying personal equations were scattered at random over the map of England, the chance of obtaining the difference in question would be about 1 in 22.

[5] i.e. does not exceed three times its probable error.

public elementary schools, excluding London, was in 1923–4, 535,689, and therefore in the area covered by the survey this total may be estimated at 485,500. It therefore follows that 375,022 out of a possible 485,500, or 77 per cent. of all the children on the registers, were actually examined in the areas where the survey was carried out by the school medical officers; the survey of this age group was therefore remarkably complete.

Assessment of the Personal Factor in a Sample Area.

Since the time which could be devoted to actual field-work on this question was naturally limited, the choice lay between adopting the expedients here used to estimate the probable errors of rates due to personal equation, and putting aside the whole of the results of the survey as useless for comparative purposes. Had I not felt confident, however, that the assumptions and approximations of necessity employed do not introduce inaccuracies serious enough to invalidate the conclusions based on them, this paper would not have been published. In the first place the problem is not a simple one, because a given personal equation in judging at what point enlargement begins will have a different effect on the resulting goitre rate in districts with different goitre prevalence. To make this clear, the personal factor is the limiting size of the thyroid gland at which the observer considers that normality ceases; each observer has his own idea as to what constitutes normality in the size of the gland, and begins to record enlargements at a more or less definite point in the scale of size. The observer's *personal equation* is best measured by the deviation of his limiting point from that of the 'mean observer'. Since I have shown elsewhere[6] that the linear measurement of maximum thyroid breadth gives the highest correlation with visual estimates of size, and since it is also the simplest measure of thyroid size to make in practice, I have used a scale of thyroid breadth on which to measure all the personal equations. Then, if x_1 cm. be the limiting breadth for a medical officer M_1, and $\bar{x}$ the mean limiting breadth for all medical officers, the personal equation of M_1 is given by

$$e_1 = x_1 - \bar{x} \qquad . \quad . \quad . \quad . \quad . \quad . \qquad (1)$$

and may be positive or negative in sign according to whether M_1 considers enlargement to commence at a greater or smaller breadth than does the average medical man.

In a paper in *Biometrika*[7] I have analysed a series of measurements I made on some 540 girls aged 11–13 in Cheshire and London, and 540 boys aged 11–13 in Devonshire and Denbighshire. In that work two methods were used concurrently:

(i) Classification of the size of the thyroid gland into three categories, defined as follows:

Category 01. Thyroids which presented no visible enlargement on inspection (those of subgroup 0 being also impalpable).

[6] See Reference No. 3. [7] Ibid.

Category 2. Thyroids visibly enlarged but not sufficiently so to produce gross deformity in the shape of the neck.

Category 3. Thyroids enlarged sufficiently to be termed 'goitre' beyond question.

In this classification the boundary between Categories 01 and 2 corresponds to my own interpretation of the definition used in the school medical officers' survey.

(ii) Measurement of the maximum breadth of the gland by an instrument with sliding points held in the right hand whilst the limits were defined by the thumb and forefinger of the left hand, using only sufficient pressure to define those limits.

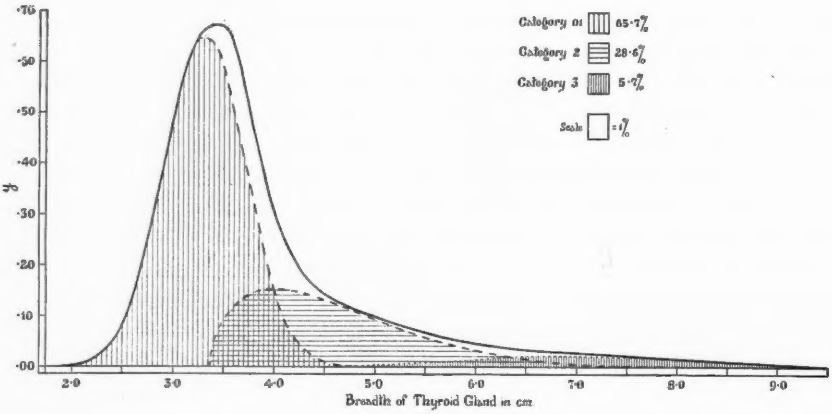

FIG. 1.

Mathematical curves were then fitted to the frequency distributions of thyroid breadth for boys and girls separately in each of the three categories, and their formulae are set out in equations (1), (2), and (3) of the paper referred to. For brevity we will call them here

Category 01, $y_1 = f_1(x)$; Category 2, $y_2 = f_2(x)$; Category 3, $y_3 = f_3(x)$;

where x is the thyroid breadth in cm., and y is the ordinate of the curve, the total frequency or area of the curve being unity in each case. The values of the ordinates y_1, y_2, y_3 are set out in Table I at millimetre intervals of x, and these are sufficient for the purposes of this paper. The three curves for girls are drawn in Fig. 1, their areas being there proportional to the frequencies of the categories which I found in a school at Exeter, the total area of the three combined being unity on the scale used in the diagram.

If we assume that the form of the curve for each category does not change with goitre prevalence, the total distribution of thyroid breadths in any population of girls can be deduced if only the proportions in which the three categories occur have been determined. Thus if these proportions be γ_1, γ_2, and γ_3, where

$\gamma_1 + \gamma_2 + \gamma_3 = 1$ (i.e. 100 γ_1 would be the percentage of girls with 'normal' thyroids), the frequency curve of thyroid breadth x in the population is given by

$$y = \gamma_1 y_1 + \gamma_2 y_2 + \gamma_3 y_3 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where y is the ordinate for unit total frequency (or area). The complete curve thus deduced for the Exeter girls is shown in Fig. 1, and is simply the sum of the three component curves. The assumption here made that the form of distribution within each category remains fixed cannot of course be strictly true, and is merely an approximate expedient, but various checks which have been made on it [8] indicate that it is a sufficiently close approximation for the purpose in view.

TABLE I.

Ordinates of Component Curves of Thyroid Breadth for the Three Categories.

'Thyroid' Breadth x (cm.).	Girls.				Boys.			
	y_1.	y_2.	y_3.	$0{\cdot}818\,y_2 + 0{\cdot}182\,y_3$.	y_1.	y_2.	y_3.	$0{\cdot}98\,y_2 + 0{\cdot}02\,y_3$.
2	0·0049	—	—	—	0·0016	—	—	—
2·2	0·0217	—	—	—	0·0090	—	—	—
2·3	0·0416	—	—	—	0·0190	—	—	—
2·4	0·0752	—	—	—	0·0377	—	—	—
2·5	0·1278	—	—	—	0·0700	—	—	—
2·6	0·2044	—	—	—	0·1221	—	—	—
2·7	0·3074	—	—	—	0·1986	—	—	—
2·8	0·4348	—	—	—	0·3047	—	—	—
2·9	0·5786	—	—	—	0·4373	—	—	—
3·0	0·7245	—	—	—	0·5886	—	—	—
3·1	0·8532	—	—	—	0·7423	—	—	—
3·2	0·9453	—	—	—	0·8780	—	—	—
3·3	0·9852	—	—	—	0·9738	—	—	—
3·4	0·9660	0·1589	0·0014	0·1303	1·0130	—	—	—
3·5	0·8910	0·3342	0·0019	0·2737	0·9872	—	—	—
3·6	0·7731	0·4256	0·0026	0·3486	0·9024	—	—	—
3·7	0·6310	0·4804	0·0034	0·3936	0·7711	0·1926	—	0·1887
3·8	0·4845	0·5126	0·0045	0·4201	0·6213	0·4154	—	0·4071
3·9	0·3500	0·5290	0·0059	0·4338	0·4678	0·5836	0·0001	0·5719
4·0	0·2378	0·5337	0·0076	0·4380	0·3309	0·6955	0·0001	0·6816
4·1	0·1520	0·5296	0·0097	0·4350	0·2187	0·7582	0·0001	0·7430
4·2	0·0914	0·5189	0·0124	0·4268	0·1360	0·7809	0·0002	0·7653
4·4	0·0275	0·4834	0·0196	0·3990	0·0431	0·7415	0·0006	0·7267
4·6	0·0065	0·4365	0·0300	0·3626	0·0106	0·6381	0·0014	0·6253
4·8	0·0010	0·3841	0·0444	0·3223	0·0020	0·5123	0·0033	0·5022
5·0	0·0002	0·3304	0·0635	0·2819	0·0003	0·3894	0·0073	0·3817
5·5	—	0·2064	0·1471	0·1956	—	0·1611	0·0390	0·1587
6·0	—	0·1119	0·2527	0·1375	—	0·0515	0·1371	0·0532
6·5	—	0·0509	0·3523	0·1057	—	0·0125	0·3130	0·0186
7·0	—	0·0179	0·3986	0·0871	—	0·0022	0·4861	0·0119
7·5	—	0·0014	0·3660	0·0700	—	0·0002	0·4904	0·0100
8·0	—	0·0004	0·2728	0·0499	—	—	0·3268	0·0065
8·5	—	—	0·1650	0·0300	—	—	0·1435	0·0029
9·0	—	—	0·0810	0·0147	—	—	0·0416	0·0008

Having thus obtained a means of calculating the approximate frequency curve of thyroid breadth in any sample of children by rapidly classifying them into the three categories, it became possible to apply this to the personal equation problem in the following way:

[8] See section (3) of Reference No. 3.

TABLE II.

Analysis of Survey of 2,956 Children aged 11–13 carried out in conjunction with Nineteen School Medical Officers of Somersetshire and Devonshire—Frequencies found by Author.

Localities where Schools were surveyed.	Aged 11.			Aged 12.			Aged 13.			Proportion of total examined who showed Thyroid Enlargement of any Degree (Categories 2 and 3).				Proportion of total examined who had Pronounced Goitre (Category 3).				Proportion of total showing Thyroid Enlargement who had Pronounced Goitre.			
	Examined.	Category 2.	Category 3.	Examined.	Category 2.	Category 3.	Examined.	Category 2.	Category 3.	Aged 11.	Aged 12.	Aged 13.	Mean Rate.	Aged 11.	Aged 12.	Aged 13.	Mean Rate.	Aged 11.	Aged 12.	Aged 13.	Mean Rate.
Girls.																					
Bath	23	4	—	116	27	4	115	25	—	0·174	0·267	0·217	0·2195	—	0·034	—	0·0115	—	0·129	—	0·0430
Farnham	66	14	—	51	8	2	46	13	1	0·212	0·196	0·304	0·2375	—	0·039	0·022	0·0203	—	0·200	0·071	0·0905
Barn-staple	53	10	1	37	9	2	42	7	3	0·208	0·298	0·238	0·2476	0·019	0·054	0·071	0·0481	0·091	0·182	0·300	0·1909
Bridg-water	59	14	2	40	10	—	50	12	1	0·271	0·250	0·260	0·2604	0·034	—	0·020	0·0180	0·125	—	0·077	0·0673
Plymouth	62	16	—	52	9	2	36	10	2	0·258	0·212	0·333	0·2677	—	0·038	0·056	0·0313	—	0·182	0·167	0·1162
Torquay	47	11	2	57	15	2	61	9	3	0·276	0·298	0·197	0·2905	0·042	0·035	0·049	0·0423	0·154	0·118	0·250	0·1738
Exeter	58	19	1	38	10	2	30	8	3	0·345	0·316	0·367	0·3424	0·017	0·053	0·100	0·0566	0·050	0·167	0·273	0·1631
Taunton	47	13	3	36	11	1	36	10	3	0·340	0·333	0·361	0·3449	0·064	0·028	0·083	0·0581	0·187	0·083	0·231	0·1672
Tiverton	38	14	—	39	10	2	40	10	8	0·368	0·308	0·450	0·3754	—	0·051	0·200	0·0838	—	0·167	0·444	0·2037
Oke-hampton	24	11	1	20	4	5	21	10	4	0·500	0·450	0·667	0·5389	0·042	0·250	0·190	0·1607	0·083	0·556	0·286	0·3082
Totals and mean rates	477	126	10	486	113	22	477	114	28	0·2952	0·2928	0·3394	0·3125	0·0218	0·0582	0·0791	0·0531	0·0690	0·1784	0·1899	0·1524

Boys.																					
Bath	56	6	—	73	6	1	113	7	—	0·107	0·096	0·062	0·0883	—	0·014	—	0·0028	—	0·143	—	0·0477
Farnham	44	11	—	56	10	—	56	11	—	0·250	0·179	0·196	0·2083	—	—	—	—	—	—	—	—
Barn-staple	61	9	—	40	8	—	51	3	—	0·147	0·200	0·059	0·1354	—	—	—	—	—	—	—	—
Bridg-water	48	13	—	64	12	—	38	8	—	0·271	0·187	0·210	0·2229	—	—	—	—	—	—	—	—
Plymouth	69	7	—	48	11	—	47	9	—	0·101	0·229	0·191	0·1740	—	—	—	—	—	—	—	—
Torquay	69	14	—	52	7	—	50	9	—	0·203	0·135	0·180	0·1725	—	—	—	—	—	—	—	—
Exeter	51	16	—	65	15	1	49	10	—	0·314	0·246	0·204	0·2547	—	0·015	—	0·0051	—	0·062	—	0·0207
Taunton	28	9	—	36	11	—	27	5	—	0·321	0·306	0·185	0·2707	—	—	—	—	—	—	—	—
Tiverton	52	11	—	41	11	—	61	12	2	0·212	0·268	0·230	0·2364	—	—	0·033	0·0109	—	—	0·143	0·0477
Oke-hampton	19	4	—	22	9	—	30	11	—	0·210	0·409	0·273	0·2974	—	—	—	—	—	—	—	—
Totals and mean rates	497	100	—	497	100	2	522	85	2	0·2136	0·2255	0·1790	0·2061	—	0·0029	0·0033	0·0021	—	0·0205	0·0143	0·0116

With the co-operation of the Medical Department of the Board of Education and of Dr. W. G. Savage and Dr. George Adkins, the county medical officers of Somerset and Devon, I met nineteen of the school medical officers who were concerned in the 1924 survey in those counties at various schools, and examined approximately 300 children in company with each of them. By meeting several medical officers of adjoining districts simultaneously, this was done in ten separate inspections, though in some instances visits to several neighbouring schools were necessary to provide enough children for an inspection.[9] The proceeding was as follows: each medical officer was asked to use the same standard in assessing thyroid enlargement as he used in 1924; the children passed in front of each of us in succession and we recorded the numbers exhibiting thyroid enlargement without comparing notes until all were completed. At the same time I recorded the numbers in the three categories, using the same standards of division as I had used in the other work. Each age group 11, 12, and 13 of boys and girls was recorded separately by each medical officer, and approximately 3,000 children in all were examined.

The results as recorded by myself are analysed in Table II. The rates of enlargement at each age, 11, 12, 13, were computed separately for each medical officer and the mean of the three rates taken as basis on which to work; these mean rates are shown in Table III. The mean rates found by myself in each category are given in Table II; thus for girls aged 11–13 in the Exeter schools the mean rate in categories 2 + 3 was 0·3424, leaving 0·6576 in category 01, hence $\gamma_1 = 0{\cdot}6576$; another column gives γ_3 as 0·0566, hence $\gamma_2 = 0{\cdot}2858$ by subtraction. These values of γ_1, γ_2, γ_3 are also given in Table XX, and they are the values used in constructing Fig. 1 by means of equation (2) and Table I; a slight smoothing is called for at the crest of the curve, but the effect of this on any calculations would be negligible where γ_1 exceeds 0·5 (50 per cent. normal).

Now the area enclosed by this curve, the base line, and two vertical ordinates at points x_1 and x_2 is equal to the fraction of girls per unit who would be expected to have thyroids with breadths between the limits x_1 cm. and x_2 cm., and the area overlying the base line from a point x_1 to infinity gives the rate of thyroid enlargement above a limiting thyroid breadth of x_1 cm. in the population for which the curve was drawn. The values of x were therefore computed by equating the frequencies or areas of the appropriate composite curves overlying the base line from a point x to infinity in turn to the various goitre rates found by the medical officers taking part in the test, as shown in Table III. Thus,

[9] These inspections were done at Taunton, Bridgwater, Exeter, Tiverton, Barnstaple, Okehampton, Plymouth, Torquay, and Bath, and the medical officers who kindly took part were Drs. Dunscombe, Hibbert, Parker, and Walker of Somerset County, Drs. Baxendell, Corkery, Hosegood, Painton, Scott, and Straton of Devon County, Dr. Allen (Taunton), Dr. Bird (Bridgwater), Dr. Burgess (Tiverton), Dr. Cole (Plymouth), Dr. Gibbs (Barnstaple), Dr. Matthews (Exeter), Dr. Simpson (Torquay), and Dr. Thomas (Bath). Dr. Butcher, who was working in the Yeovil area of Somerset in the 1924 survey and is now in Surrey County, kindly met me at Farnham in that county in order to complete the standardization of the Devon and Somerset returns.

TABLE III.

Calculation of the Extent of the Personal Equation in estimating Frequencies of Visible Thyroid Enlargement according to the Definition used in 1924.

Localities where Schools were surveyed.	Girls. Proportions of total examined who had Thyroid Enlargement: According to Author. A.*	Girls. According to other M.O.'s.†		Girls. Limiting Thyroid Breadth corresponding to these Frequencies on Composite Curve: Author's Value.‡	Girls. Values for other M.O.'s.‡	Girls. Deviation from Author's Limiting Point.	Girls. Square of Deviation.	Boys. Proportions of total examined who had Thyroid Enlargement: According to Author. A.*	Boys. According to other M.O.'s.†		Boys. Limiting Thyroid Breadth corresponding to these Frequencies on Composite Curve: Author's Value.‡	Boys. Values for other M.O.'s.‡	Boys. Deviation from Author's Limiting Point.	Boys. Square of Deviation.
Bath	0·2195	B	0·1415	3·934	4·260	+0·326	0·1062	0·0883	B	0·0599	4·173	4·353	+0·180	0·0324
	—	C	0·1040	—	4·566	+0·632	0·3994	—	C	0·0435	—	4·528	+0·355	0·1260
Farnham	0·2375	D	0·3085	3·924	3·762	−0·162	0·0262	0·2083	D	0·2457	4·056	3·962	−0·094	0·0088
Barnstaple	0·2476	E	0·2006	3·934	4·106	+0·172	0·0296	0·1354	E	0·0875	4·114	4·340	+0·226	0·0511
	—	F	0·1115	—	4·864	+0·930	0·8649	—	F	0·0237	—	5·064	+0·950	0·9025
Bridgwater	0·2604	G	0·3487	3·904	3·717	−0·187	0·0350	0·2229	G	0·1570	4·046	4·259	+0·213	0·0454
	—	H	0·1642	—	4·282	+0·378	0·1429	—	H	0·2229	—	4·046	0·000	0·0000
	—	I	0·3959	—	3·639	−0·265	0·0702	—	I	0·2251	—	4·040	−0·006	0·0000
Plymouth	0·2677	J	0·2583	3·906	3·932	+0·026	0·0007	0·1740	J	0·0989	4·080	4·403	+0·323	0·1043
	—	K	0·2314	—	4·016	+0·110	0·0121	—	K	—	—	—	—	—
Torquay	0·2905	L	0·2394	3·895	4·054	+0·159	0·0253	0·1725	L	0·2320	4·081	3·929	−0·152	0·0231
	—	M	0·2109	—	4·176	+0·281	0·0790	—	M	0·2284	—	3·937	−0·144	0·0207
Exeter	0·3424	N	0·1515	3·864	4·825	+0·961	0·9235	0·2547	N	0·1317	4·029	4·464	+0·435	0·1892
	—	O	0·3364	—	3·879	+0·015	0·0002	—	O	0·2811	—	3·966	−0·063	0·0040
	—	P	0·4133	—	3·715	−0·149	0·0222	—	P	0·2297	—	4·095	+0·066	0·0044
Taunton	0·3449	Q	0·2092	3·863	4·497	+0·634	0·4020	0·2707	Q	0·1248	4·018	4·523	+0·505	0·2550
	—	R	0·4147	—	3·716	−0·147	0·0216	—	R	0·3902	—	3·779	−0·239	0·0571
Tiverton	0·3754	S	0·3399	3·854	3·949	+0·095	0·0090	0·2364	S	0·1602	4·043	4·297	+0·254	0·0645
Okehampton	0·5389	T	0·5131	3·775	3·837	+0·062	0·0038	0·2974	T	0·1863	4·004	4·322	+0·318	0·1011
Mean values	—		—	3·885	—	+0·1935 §	—	—		—	4·064	—	+0·1646 ‖	—

* Mean rate for ages 11, 12, 13, i.e. $(\gamma_2+\gamma_3)$. † Mean rate for ages 11, 12, 13 as found by M.O. in question in the same children.

‡ i.e. values of x (thyroid breadth in cm.) at which areas of composite curve $y = \gamma_1 y_1 + \gamma_2 y_2 + \gamma_3 y_3$ from x to infinity = rates in preceding columns.

§ Mean for 20 observers including author. ‖ Mean for 19 observers including author.

taking Exeter as example, four medical officers, P. S., N, O, and P, examined simultaneously girls aged 11–13, and the rates they found were:

P. S. 0·3424. N. 0·1515. O. 0·3364. P. 0·4133;

which means that in this particular experiment personal equation was responsible for a variation in goitre rate recorded between 15 per cent. and 41 per cent. My own figure 0·3424 was made up of 0·2858 in category 2 and 0·0566 in category 3; so having calculated the y-ordinates at millimetre intervals of x by means of equation (2), Table I, and $\gamma_1 = 0{\cdot}6576$, $\gamma_2 = 0{\cdot}2858$, $\gamma_3 = 0{\cdot}0566$, the four values of x were computed for which the areas from infinity to x were 0·3424, 0·1515, 0·3364, and 0·4133 respectively. The resulting values represent the limiting thyroid breadth between 'normal' and 'enlarged' as used by these four observers and were as follows:

P. S. 3·864 cm. N. 4·825 cm. O. 3·879 cm. P. 3·715 cm.

The same process was followed for the results of each inspection and the critical x values determined for twenty medical officers. The limiting values of x found from my rates in the ten schools show small variations about a mean value 3·8853 as shown in Table III. Using my own value as arbitrary origin, each medical officer's personal *difference* from myself was therefore found by subtracting his value of x from my own at the same inspection, and these resulting 'deviations from author's limiting point' are given in Table III. Summing these personal differences for the twenty observers (including myself with a zero difference) we obtain a mean personal difference, from my own points as origin each time, of + 0·1935 cm., and a standard deviation [10] about this mean equal to ·3482 cm.

Now, the mean limiting value for myself being 3·8853 cm., the limiting value for the *mean observer* was therefore 3·8853 + 0·1935, that is $\bar{x} = 4{\cdot}0788$ cm. The probable error of this due to random choice of observers would be $\pm 0{\cdot}0525$.[11] Measuring now from this mean observer's limiting point as origin, my own personal equation becomes − 0·1935 cm., and any other medical officer's personal equation is arrived at by subtracting 0·1935 cm. from his 'deviation' as shown in Table III. The standard deviation 0·3482 cm. is likewise the *standard deviation of the personal equation*, which we may denote by σ_ϵ; since its estimation is based on twenty observers only it has a profitable error $\pm 0{\cdot}0371$ cm. Proceeding in exactly the same way with the data for *boys* as shown in Table III the mean observer's limiting point is $4{\cdot}0644 + 0{\cdot}1656 = 4{\cdot}2290$ cm., my personal equation for boys being $-0{\cdot}1656$ cm., and the standard deviation of the personal equations is $0{\cdot}2786 \pm 0{\cdot}0305$. To summarize these results, we have

Mean observer's limiting point on a scale of thyroid breadth at which he considers that enlargement commences at age 12	Boys. $\bar{x} = 4{\cdot}229$ cm.	
	Girls. $\bar{x} = 4{\cdot}079$ cm.	
Standard deviation of the personal equation of medical officers	Boys. $\sigma_\epsilon = 0{\cdot}279 \pm 0{\cdot}030$ . . .	(3 *a*)
	Girls. $\sigma_\epsilon = 0{\cdot}348 \pm 0{\cdot}037$ . . .	(3 *b*)

[10] Square root of the sum of the squares of the deviations from the mean.

[11] Hence any breadth between 3·95 cm. and 4·20 cm. could be reasonably used.

Effect of Locality on the Form of Frequency Distribution.

The thyroid problem is peculiar in this respect, that goitre is rare in early childhood, and every large goitre subsequently arising has started from normality and passed slowly through the intermediate stages of size, so that in large groups of children about age 12 living in districts with stationary goitre prevalence it is therefore reasonable to suppose that each large goitre will be accompanied by a fairly constant proportion of the smaller degrees of goitre; that is to say, that in places where the stimulus to enlargement has for a long period been operative, and not more than, say, 50 per cent. of children [12] are affected to any degree, all degrees of thyroid enlargement will be found to be proportionately increased. This would not be true if so-called 'physiological enlargements' were fundamentally different in origin to the ordinary goitres, but the evidence in this section and pp. 242–6 seems to discount such an idea.[13] If the hypothesis were strictly true, and if the beginnings of enlargement truly corresponded to the boundary between my categories 01 and 2, then the method here used would be free from objection; that it can only be approximately true is realized, but in view of the evidence which follows and the checks which have been applied, the hypothesis is believed to be near enough to the truth for the purposes of this paper. In Table II are given the ratios of children in categories 2 + 3 to the totals examined in the Devon and Somerset schools; also the proportions examined who were in category 3. The last four columns give the ratios of large goitres to total enlargements of any degree, that is, the ratios of category 3 to categories 2 + 3. The localities are arranged in order of increasing mean total rate of enlargement in girls, and a glance at the figures in the last column rather suggests that the ratio of large to total goitres also increases as the total rate increases, but this is not borne out by the additional evidence given below, which indicates that the ratio between categories 2 and 3 does not change appreciably until very high rates of goitre are reached, as at Okehampton possibly in the Devonshire data. The numbers on which the ratios in the last column are calculated are necessarily small, averaging 35 to each group, hence their probable errors are of the order 0·05, so that with the possible exception of Okehampton the ratios do not differ significantly from the mean ratio 0·15.

I have collected the following evidence on this point. (*a*) From *Cheshire*, where the ratios of large to total goitres are from my own observations and exactly comparable with those of Table II, we have the following figures. The total goitre frequencies are obtained from a routine survey of the same schools by Dr. A. V. Stocks in 1924–5, and a comparison of the standards used by him and by myself in a simultaneous work on 450 girls proved that the difference in personal equation was very small. Dividing the Cheshire schools visited into four areas of different goitre prevalence, and giving mean rates for ages 11, 12, 13:

[12] When a saturation point is approached, as at some places in Switzerland, the proportionality would be expected to change.

[13] See also Reference No. 3.

	A.	B.	C.	D.
Proportion of large (category 3) to total goitres (categories 2 + 3)	0·1904	0·2311	0·1606	0·1647
Proportion of total enlargements to total girls examined	0·0975	0·0897	0·1649	0·2083

A = Altrincham. B = Runcorn, Stockton Heath, Lymm. C = Northwich area. D = Knutsford and Halton.

Although we are here dealing with districts having rates of thyroid enlargement of the order 0·1 to 0·2 and therefore considerably less than in Devon and Somerset, the ratio of category 3 to categories 2 + 3 is, if anything, slightly greater, averaging 0·18.

(*b*) The following figures are taken from the report of the school medical officer for *Shropshire* for 1914, p. 35, the classification into 'marked' and 'slight' being of course not necessarily comparable with my own. The total children examined in the year were 7,385. The sixteen areas have been arranged in order of increasing goitre prevalence in Table IV; the mean total goitre rate in the first eight localities is 0·058 and in the last eight it is 0·122; the mean ratio of 'marked' goitres to all goitres is 0·122 in the first eight and 0·123 in the second eight; hence there is here no evidence of any consistent change in the ratio with increasing total rate of thyroid enlargement.

TABLE IV.

Shropshire Figures, 1914.

District.	Proportion of Children with 'Marked' Goitre.	Proportion with any Degree of Goitre.	Ratio of 'Marked' to all Goitres.
Church Stretton	0·000	0·032	0·000
Wellington	0·010	0·049	0·204
Bishop's Castle	0·012	0·054	0·222
Ludlow	0·007	0·055	0·127
Condover	0·011	0·059	0·186
Cleobury Mortimer	0·007	0·061	0·115
Bridgnorth	0·001	0·066	0·015
Albrighton	0·010	0·091	0·110
Oswestry	0·008	0·101	0·079
Whitchurch	0·015	0·106	0·142
Shifnal	0·013	0·119	0·109
Wem	0·019	0·122	0·156
Newport	0·016	0·126	0·127
Ellesmere	0·013	0·126	0·103
Drayton	0·021	0·135	0·156
Pontesbury	0·016	0·138	0·116

(*c*) There is some evidence to be obtained from *Swiss* figures due to H. Kerzmann and Professor de Quervain,[14] which provide a comparative survey in three districts, made according to the standards laid down by the Swiss Goitre Commission. I give here the proportions of boys and girls examined who were classed in the groups 'Category II and upwards' and 'Category III and upwards' and the ratios between these two measures of goitre prevalence. All the rates are mean rates for the ages 11, 12, and 13.

[14] See Reference No. 4.

	Boys. II–	Boys. III–	Boys. Ratio.	Girls. II–	Girls. III–	Girls. Ratio.	Mean Rates. II–	Mean Rates. III–	Mean Rates. Ratio.
La Chaux de Fonds	0·324	0·175	0·540	0·489	0·348	0·712	0·406	0·261	0·626
Le Locle	0·548	0·336	0·613	0·630	0·395	0·627	0·589	0·365	0·620
Neuchâtel	0·583	0·355	0·609	0·750	0·417	0·556	0·666	0·386	0·582

The mean rates for boys and girls again indicate no tendency for the ratio of large to large and small goitres to increase when the total rate changes from 40 to 60 per cent.; if anything the ratio seems to decline in girls. The corresponding mean ratio for Berne, which had a goitre rate as high as 88 per cent. by the first criterion, was 0·689, which may indicate an increase in the ratio for very high rates, as might be expected when 'saturation point' is being approached.

(*d*) In the *United States of America* several surveys of school children have been carried out by R. Olesen, which provide data for this purpose. From three reports published in 1924, 1925, and 1926, relating respectively to Minnesota,[15] Colorado,[16] and Connecticut,[17] I have extracted the following relevant figures relating to 9,836 girls in all. A division into three grades of thyroid enlargement, termed 'slight', 'moderate', and 'marked', was used in the surveys; an additional group, 'very slight', used in one survey I have treated as normal. I have divided the localities into groups according to the percentages of girls examined who were classed from 'slight' upwards, and have then calculated the ratios of moderate and marked goitres to the totals showing slight, moderate, or marked enlargement. The results are given in Table V.

TABLE V.

Localities.	Percentage of Girls showing Enlargement, Slight, Moderate, or Marked. Group Limits.	Percentage of Girls showing Enlargement, Slight, Moderate, or Marked. Mean of Group.	Total Girls examined.	No. with 'Slight' Goitre.	No. with 'Moderate' or 'Marked' Goitre.	Ratio of Moderate + Marked to all Degrees of Enlargement.
Connecticut, 17 districts	0–10	5·34	4545	203	40	$0·165 \pm 0·016$
Connecticut, 11 districts	10–20	13·28	2063	223	51	$0·186 \pm 0·016$
Colorado, Telluride	50–60	59·62	104	53	9	$0·145 \pm 0·030$
Minnesota, St. Peter	50–60	51·48	202	92	12	$0·115 \pm 0·021$
Colorado, 3 districts	60–70	63·77	345	189	31	$0·141 \pm 0·015$
Minnesota, 4 districts	60–70	66·93	995	457	209	$0·314 \pm 0·012$
Colorado, Durango	70–80	73·21	112	59	23	$0·280 \pm 0·033$
Minnesota, 5 districts	70–80	75·03	737	369	184	$0·333 \pm 0·014$
Colorado, 3 districts	80–90	86·17	376	154	170	$0·525 \pm 0·019$
Minnesota, 3 districts	80–90	84·88	357	159	144	$0·475 \pm 0·019$

[15] See Reference No. 5. [16] See Reference No. 6. [17] See Reference No. 7.

It appears that the ratio of moderate + large goitres to total thyroid enlargements shows no significant tendency to increase until the total rate has exceeded 60 per cent. This is in fair agreement with my own observations and the Swiss figures.

(*e*) More precise evidence can be obtained by comparing actual distributions of the visibly enlarged thyroids on a scale of thyroid breadth or superficial area [18] for several districts. I have here used the latter as a measure of thyroid size in order to compare the Cheshire data with a table given by Hunziker relating to a series of girls measured in Swiss schools where the goitre frequency was high (certainly not less than 50 per cent. on the standard chosen). The frequency beyond the boundary 10 sq. cm. of thyroid area has been taken as the total with visible enlargement in this table, the basis for this being that 10 sq. cm. corresponds approximately with my limiting value of 3·88 cm. of thyroid breadth found on page 232), since the average height of the lobes is about 2·6 cm. I have again taken four groups of Cheshire schools, separating ages 11–12 and 13–14, the rates in the first two lines of Table VI being derived from the survey by Dr. A. V. Stocks [19] as explained in (*a*) above. The test applied has been to calculate the proportions of the total girls with enlarged thyroids, measured by myself [20] in each of the localities A, B, C, D and by Dr. Hunziker in locality E, whose thyroids had a superficial area exceeding 30 sq. cm.

TABLE VI.

	Ages.	Locality. A.	B.	C.	D.	E.
Proportion of girls in the schools with thyroid enlargement (categories 2+3)	11–12	0·063	0·098	0·144	0·229	Over 0·5
	13–14	0·167	0·072	0·207	0·167	
Total girls in these categories who were measured	11–12	26	40	43	20	89
	13–14	31	50	60	21	47
Proportion of these girls with thyroid area exceeding 30 sq. cm.	11–12	0·11	0·12	0·12	0·10	0·11
	13–14	0·26	0·16	0·25	0·25	0·23
Mean thyroid area for girls in categories 2+3 (sq. cm.)	11–12	17·1	19·4	19·7	16·9	21·8
	13–14	23·0	21·4	22·7	23·7	23·8
Standard deviation of the distributions of thyroid area (sq. cm.)	11–12	7·8	10·0	9·5	11·2	—
	13–14	9·0	10·6	12·2	11	—

A = Altrincham. B = Runcorn, Stockton Heath, Lymm. C = Northwich area.
D = Knutsford and Halton. E = Hunziker's data.

The proportions with thyroid area above the arbitrary limit of 30 sq. cm., in the fifth and sixth lines of Table VI, are remarkably uniform, though the goitre

[18] See Reference No. 3 for a discussion of this measure used by Hunziker; it is the product of the maximum breadth of the gland and the mean height of the two lobes.

[19] See Reference No. 8.

[20] The reason for this is that my method in Cheshire was to first select for measurement all the girls presenting any degree of enlargement, and then to measure a random sample of the normals; hence this work did not give the total enlargement rate in the school.

prevalence in the five districts ranges from 6 to 50 per cent. or more. The probable errors of the mean areas are of the order 1 sq. cm., so these do not differ significantly.

In view of the cumulative evidence in (*a*) to (*e*) above, we may assume that the large goitres would, in large enough samples, form a fairly constant fraction of the total enlargements in different localities where not more than about 50 per cent. of girls are affected, provided that actual measurements are used to define these terms, or that observations are made by the same observer throughout. For my own delimitation of the large from the small goitres this ratio of category 3 to categories $2+3$ may be taken as $2:11$ or 0·182 for a population of girls aged 12. The Devon and Somerset figures in Table II gave for age 12 the value 0·178 and the Cheshire figures 0·182; for age 13 the value was slightly higher. For boys the ratio was much smaller, and may be taken as $1:50$ or 0·02 at age 12.

The distribution of thyroid breadth in any population of boys or girls aged 12 can on this assumption be roughly determined, if only the rate of thyroid enlargement according to my own standard be known. Thus if g_0 be this rate in *boys* aged 12 in a locality, the proportions in categories 01, 2, and 3 are given by $1-g_0$, $0{\cdot}98\,g_0$, and $0{\cdot}02\,g_0$ respectively, and the frequency distribution on a scale of thyroid breadth is given by

$$y = y_1(1-g_0)+0{\cdot}98\,y_2\,g_0+0{\cdot}02\,y_3\,g_0\,y_2 \quad . \quad . \quad . \quad . \quad . \quad (4\,a)$$

where y is the ordinate for unit total frequency and y_1, y_2, y_3 are given in Table I for different values of the thyroid breadth x. For *girls* aged 12 the corresponding distribution in a locality with thyroid rate g_0, according to my own standard, is

$$y = y_1(1-g_0)+0{\cdot}818\,y_2\,g_0+0{\cdot}182\,y_3\,g_0 \quad . \quad . \quad . \quad . \quad . \quad (4\,b)$$

The kind of change which takes place in the complete distribution of thyroid breadths as goitre prevalence increases is illustrated by a series of hypothetical curves reproduced in Fig. 4 of a paper in *Biometrika*[21] which are based upon the evidence collected in this section.

Effect of the Personal Equation on Goitre Rates.

In the 1924 survey by the school medical officers, 375,022 may be taken as the total 12-year-old children examined after eliminating some uncertain figures, and as shown on pp. 224–5 this total formed about 77 per cent. of the total on the registers at that age. The number of medical officers taking part is estimated at 606, so that on the average each examined about 620 children. In view of these facts the errors in the goitre rates due to sampling of the children will be very small in comparison with the errors due to personal equation, and may be neglected.

In a county area surveyed by n medical officers examining a total of $S(N)$

[21] See Reference No. 3.

girls, where S represents summation for the n districts and N the number of girls examined in a single district, suppose the aggregate goitre rate per unit derived by putting together all their figures to be G, and the true goitre rate which would have been found by a single observer with zero personal equation (the 'mean observer') to be G'. Then on the assumption that the number of girls N examined by any medical officer M bore a constant ratio to the total population of girls in his district, it can be shown that

$$G = G' + \frac{S[(N)(g-\bar{g})]}{S(N)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where g is the goitre rate actually returned by M from his examination of the N girls, and $\bar{g}$ is the goitre rate which would have been found by the mean observer in those N girls.

On the assumption that the numbers examined had no real correlation with the personal equations of the medical officers who examined them this leads to

$$G = G' + \frac{S(g-\bar{g})}{n} \pm 0{\cdot}6745 \frac{\sqrt{n}}{S(N)} \sigma_N \sigma_{(g-\bar{g})} \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where σ_N is the standard deviation of the numbers of girls examined by the several medical officers, and $\sigma_{(g-\bar{g})}$ is the standard deviation of the values $(g-\bar{g})$.

Hence the probable error of G can be shown to be

$$\pm \frac{0{\cdot}6745}{\sqrt{n}} \sigma_{(g-\bar{g})} \sqrt{1 + \left(\frac{n}{S(N)} \sigma_N\right)^2} \quad . \quad . \quad . \quad . \quad (7)$$

Since $\frac{S(N)}{n}$ is the mean value of the N's, $\frac{100n}{S(N)}\sigma_N$ is the coefficient of variation of the numbers of girls examined by individual medical officers, and since a few tests show that in the same class of area this does not differ significantly from one part of the country to another, I have evaluated it from all the areas in the returns for which separate totals for each medical officer could be ascertained, keeping separate three classes of area which have different administrative arrangements, namely (i) county areas, which are chiefly rural in character; (ii) urban districts and small boroughs with separate local education authorities; (iii) county boroughs. The frequency distributions of these three groups according to the numbers of girls and boys examined by individual medical officers were as shown in Table VII, and the means and standard deviations of the distributions are shown in Table VIII.

TABLE VII.

	Sex.	No. of Children examined by Individual M.O.'s.												
		1–	101–	201–	301–	401–	501–	601–	701–	801–	901–	1001–	1101–	1201–
County areas	M	10	13	20	12	6	5	5	1	2	2	—	—	—
	F	11	12	23	10	7	3	4	2	2	—	1	—	1
Urban districts and boroughs	M	14	36	34	14	11	1	2	1	—	—	—	—	—
	F	15	34	35	15	8	3	3	—	—	—	—	—	—
County boroughs	M	5	6	5	13	10	6	7	3	3	2	—	—	1
	F	4	8	5	12	9	11	7	1	1	2	—	1	—

TABLE VIII.

		Mean Number examined per Medical Officer.	Standard Deviation of these Numbers.
County areas	Boys	$325{\cdot}5 \pm 16{\cdot}8$	$217{\cdot}6 \pm 11{\cdot}9$
	Girls	$322{\cdot}9 \pm 18{\cdot}3$	$236{\cdot}4 \pm 12{\cdot}9$
Urban districts and boroughs	Boys	$239{\cdot}9 \pm 8{\cdot}7$	$134{\cdot}8 \pm 6{\cdot}0$
	Girls	$239{\cdot}9 \pm 8{\cdot}7$	$134{\cdot}8 \pm 6{\cdot}0$
County boroughs	Boys	$445{\cdot}6 \pm 22{\cdot}6$	$261{\cdot}5 \pm 16{\cdot}0$
	Girls	$429{\cdot}2 \pm 19{\cdot}9$	$230{\cdot}2 \pm 14{\cdot}1$

The values for boys and girls do not differ appreciably, so they have been combined in each case and the mean value used. The figures are compiled from returns relating to 250 medical officers; in the returns from many of the large administrative areas the figures for individual officers could not be separated. The resulting coefficients of variation are as follows:

		County Areas.	U. D. and Boroughs.	County Boroughs.
Total medical officers who took part		260	152	194
Number with separate returns	n	76	113	61
Mean number of boys or girls examined	$\frac{S(N)}{n}$	324	240	437
Standard deviation of numbers examined	σ_N	227	135	246
Coefficient of variation $\times \frac{1}{100} = \frac{n}{S(N)}\sigma_N$		0·700	0·563	0·563

Hence $\sqrt{1+\left(\frac{n}{S(N)}\sigma_N\right)^2}$ has the value 1·2207 for county areas and 1·1476 for other classes of area, giving for the *probable errors of G* for either boys or girls the values

$$\pm\frac{0{\cdot}8234}{\sqrt{n}}\sigma_{(g-\bar{g})} \text{ for county areas} \quad . \quad . \quad . \quad . \quad . \qquad (8)$$

$$\pm\frac{0{\cdot}7741}{\sqrt{n}}\sigma_{(g-\bar{g})} \text{ for urban districts or towns} \quad . \quad . \qquad (9)$$

We now require to express $\sigma_{(g-\bar{g})}$ in terms of the standard deviation of personal equations σ_ϵ which was evaluated in equations (3). By actual computation the areas of the curves for the three categories between the limits of thyroid breadth corresponding to my own standard (3·885 cm. for girls, 4·064 cm. for boys) and the limits deduced for the mean observer (4·079 cm. for girls, 4·229 cm. for boys) are found to be

	Category 01 Curve.	Category 2 Curve.	Category 3 Curve.
Girls	0·0503	0·1033	0·0014
Boys	0·0296	0·1269	0·0000

and hence on the basis of equations (4), if g_0 be my own estimate of goitre rate, and $\bar{g}$ that of the mean observer, for *girls*

$$g_0-\bar{g} = 0{\cdot}0503\,(1-g_0)+(0{\cdot}1033\times 0{\cdot}818)\,g_0+(0{\cdot}0014\times 0{\cdot}192)\,g_0$$

leading to $\quad g_0 = 1{\cdot}0357\,\bar{g}+0{\cdot}0521 \quad . \quad . \quad . \quad . \quad . \qquad$ (10 b)

and similarly for *boys* $\quad g_0 = 1{\cdot}1047\,\bar{g}+0{\cdot}0327 \quad . \quad . \quad . \quad . \quad . \qquad$ (10 a)

By computing in the same way the areas between the limits $\bar{x} \pm \sigma_\epsilon$ on the curves for the three categories these are found to be

	Category 01 Curve.	Category 2 Curve.	Category 3 Curve.
Girls	0·1506	0·3596	0·0071
Boys	0·0825	0·4148	0·0002

and on the basis of equations (4) the increase in goitre rate which would result by changing a personal equation from $+\sigma_\epsilon$ to $-\sigma_\epsilon$ is found to be for girls $2 \times 0{\cdot}0751\,(1{\cdot}0531 + \bar{g})$ and for boys $2 \times 0{\cdot}1790\,(0{\cdot}2600 + \bar{g})$, from which it follows by a series of approximations

that for *girls* $\sigma_{(g-\bar{g})} = 0{\cdot}0751\,(1{\cdot}0531 + G)$ . . . (11 b)

and for *boys* $\sigma_{(g-\bar{g})} = 0{\cdot}1790\,(0{\cdot}2600 + G)$ . . . (11 a)

Substituting in equations (8) and (9) we obtain the following expressions for the probable errors of a goitre rate in a region where n medical officers were concerned in the survey; the values are slightly different if we are comparing county areas to the values for towns, but in any case it will be necessary to keep separate the different classes of area owing to the connexion between goitre prevalence and urbanization.

TABLE IX. *Expressions for Probable Errors of Goitre Rates.*

County areas	Boys	$\pm \frac{0{\cdot}1474}{\sqrt{n}}(0{\cdot}2600 + G)$	$\pm \frac{0{\cdot}1474}{\sqrt{n}}(26{\cdot}0 + p)$
	Girls	$\pm \frac{0{\cdot}0618}{\sqrt{n}}(1{\cdot}0531 + G)$	$\pm \frac{0{\cdot}0618}{\sqrt{n}}(105{\cdot}3 + p)$
Urban areas and towns	Boys	$\pm \frac{0{\cdot}1386}{\sqrt{n}}(0{\cdot}2600 + G)$	$\pm \frac{0{\cdot}1386}{\sqrt{n}}(26{\cdot}0 + p)$
	Girls	$\pm \frac{0{\cdot}0581}{\sqrt{n}}(1{\cdot}0531 + G)$	$\pm \frac{0{\cdot}0581}{\sqrt{n}}(105{\cdot}3 + p)$

[n is the number of medical officers concerned in returning the aggregate rate of thyroid enlargement G, and $p = 100\,G$ = percentage rate.]

Thus if nine school medical officers were jointly responsible for returning 20 per cent. as the aggregate rate of thyroid enlargement amongst girls aged 12 in a county area, this 20 per cent. would be subject to a probable error of

$$\frac{0{\cdot}0618}{3} \times 125{\cdot}3 = 2{\cdot}57 \text{ per cent.},$$

whilst the same percentage amongst boys would be subject to a probable error of 2·27 per cent. This means that in comparing two counties with only nine medical officers each, a rate of 16 per cent. would not be significantly different from 24 per cent., but 14 per cent. would be significantly different from 26 per cent.

In comparing mixed rural and urban areas a mean value for the probable error has been used, namely, for boys $\pm \frac{0{\cdot}143}{\sqrt{n}}(0{\cdot}2600 + G)$ and girls

$$\pm \frac{0{\cdot}060}{\sqrt{n}}(1{\cdot}0531 + G).$$

All the above expressions can only be regarded as approximations, being derived by a series of assumptions which have been mentioned and, where necessary, justified in the preceding pages. I have used as criterion of significance that rates or differences between rates shall exceed three times their probable errors according to these formulae, which allows a margin of safety.

Suggested Definite Standard based on the 'Mean Observer'.

It was shown on page 232 that the mean 'limiting values' of thyroid breadth at which enlargement of the thyroid was deemed to begin according to twenty medical officers were $4{\cdot}229 \pm 0{\cdot}043$ cm. in boys and $4{\cdot}079 \pm 0{\cdot}052$ cm. in girls. A consideration of curves such as Fig. 1 and of the above figures suggests that for future work, in order to make results of different workers comparable and greatly reduce the personal factor, *enlargement of the gland shall be deemed to commence at a thyroid breadth of 42 mm. in boys and girls at the ages 11–13.*

This standard agrees with the mean opinion of twenty medical officers within the margins of probable error, and there would be very few, if any, glands with breadth exceeding this standard which would not be considered, by some observers at least, to be enlarged. It has been shown elsewhere [22] that the mean breadth of the 'normally growing' gland increases very little from age 10 to age 14 in either sex; hence the *same standard may be applied to children between their 10th and 14th birthdays* without objection.

At ages below 10 measurement of the thyroid is difficult to carry out with accuracy. At ages from 14 to 16 it changes rapidly in size in girls, and the use of a fixed standard would not be satisfactory; for boys, however, the change is so slight that the same standard might be used for comparative work up to age 16. Most future work on the thyroid in childhood will doubtless be done at ages 11–14, and I would suggest that much useful information as to the detailed geographical distribution of thyroid enlargement based on a uniform standard, and as to its relation with other factors in school hygiene, could be obtained if the school medical officers were to make use of a celluloid or cardboard 42 mm. gauge of a shape somewhat as follows:

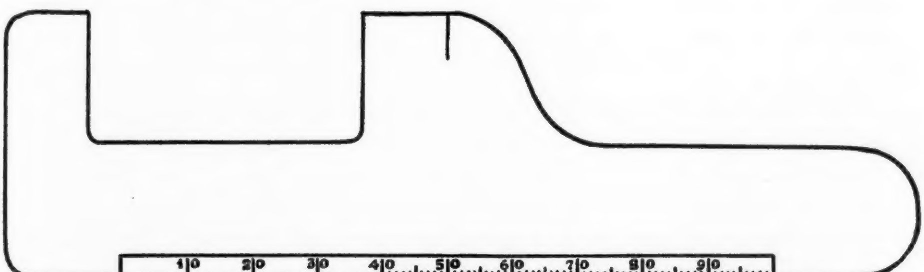

FIG. 2.

[22] See Reference No. 3.

and were asked in the course of the routine inspection of 'leavers' to ascertain, by means of this gauge, whether the maximum breadth of the gland is below or above the standard. In using the gauge the lateral limits of the gland can be defined by the thumb and forefinger of the left hand, using only sufficient pressure to so define them, and the gauge, held in the right hand, can then be brought into use, without employing more than a gentle pressure in applying the gauge to the neck. The result could be recorded on the inspection card as – or +.

The addition of a 55 mm. mark to the edge of the gauge, as shown in the drawing, would make possible, where desired, a further differentiation of the + group into moderate (+1) and marked (+2) enlargements, thus

Below 42 mm.	–	
Above 42 mm., but below 55 mm.	+1	+ if not differentiated.
Above 55 mm.	+2	

In the case of large goitres where treatment was desirable, the actual breadth could be roughly taken in order to mark progress if a millimetre scale were added to the straight edge of the gauge.

As will be seen, the personal equation in the 1924 survey makes it possible only to draw very broad conclusions as to geographical variations, but by the use of such a standard the local distribution of goitre could be worked out in much greater detail. The cost of the gauges would be trifling, and the time required to make the classification in the course of the routine inspection of 'leavers' would be small.

As an example of the grouping which would result on such a system, I give figures for unselected samples of Stockport girls and Devon boys, aged 11–13, examined by myself.

		Stockport Girls.	*Devon Boys.*	
–	Below 42 mm.	155	357	–
+1	Between 42 and 55 mm. . .	25	143	+
+2	Above 55 mm.	16		

Sex Incidence and Effect of Urbanization.

(*a*) *Sex.* Enlargement of the thyroid gland, whether slight or pronounced, is more common in women than men at all ages from childhood upwards. During the period of adolescence, the relative prevalence changes with age (see curves in Fig. 5 of Reference No. 3). It is therefore necessary, in making comparisons of sex incidence, to measure this at a special age, and I shall here confine attention to age 12. For the whole of England and Wales, the school medical officers' survey resulted as follows, the figures being the totals of Table XVIII, the probable errors being calculated by the formulae of Table IX.

TABLE X.

	County Areas.	Urban Districts and Boroughs.	County Boroughs.
No. of medical officers taking part	260	152	194
Total boys examined	78,768	39,123	70,857
No. with thyroid enlarged	2,772	1,091	990
Percentage in boys	3.52 ± 0.27	2.79 ± 0.32	1.40 ± 0.27
Total girls examined	77,633	39,194	69,447
No. with thyroid enlarged	7,097	2,818	3,215
Percentage in girls	9.14 ± 0.43	7.19 ± 0.53	4.63 ± 0.46
Ratio of girls' rate to boys' rate	2.596 ± 0.024	2.577 ± 0.018	3.307 ± 0.024

From these figures it appears that whilst the sex ratio for thyroid enlargement at age 12 is about 2·6 for the aggregates of rural areas and of small towns, it is significantly higher for the aggregate of large towns, namely 3·3. The question arises whether this is connected with the fact that the actual rate of prevalence of enlargement is in both sexes lower in towns than rural districts. To test this let us compare three large geographical areas of low, medium, and high average prevalence, namely, the districts 21 or 18, 20, and 16 as defined on page 259 and shown in Table XVIII, combining county areas with urban districts and boroughs, and keeping the county boroughs separate.

TABLE XI.

	No. of M.O.'s.	Percentage Rates. Boys.	Percentage Rates. Girls.	Ratio of Girls to Boys.
Administrative Counties:				
(16) SW. Counties	22	9.04 ± 1.07	19.24 ± 1.59	2·13
(20) E. C. and S. Midland Counties	80	4.85 ± 0.49	12.49 ± 0.79	2·57
(21) E. and SE. Midland Counties	64	1.09 ± 0.48	3.91 ± 0.82	3·59
County Boroughs:				
(20) E. C. and S. Midland Counties	33	0.93 ± 0.65	3.39 ± 1.10	3·65
(18) East Seaboard Counties	46	0.31 ± 0.54	1.40 ± 0.92	4·51

It appears that where the boys' rate is about 1 per cent., the sex ratio is about 3·5 both in the counties and county boroughs; where the boys' rate is smaller the ratio becomes higher, and as it increases to 10 per cent., the ratio diminishes to about 2.[23]

Since the sex ratio differs according to the definition of goitre used because large goitres are relatively rare in boys, comparison with data from other countries can only be of limited value. I give, however, the following relating to age 12, based on large numbers, in order to extend our range to regions of higher goitre frequency:

[23] Owing to a correlation of 0·82 between rates in boys and girls the probable errors of the ratios are much smaller than the probable errors of the individual rates due to personal equation.

TABLE XII.

		Percentage Rates. Boys.	Girls.	Ratio.
Connecticut (7)	A	1·1	4·3	3·87
	B	7·0	23·7	3·39
Cincinatti (9)	A	12·4	33·0	2·66
	B	33·1	49·6	1·50
Neuchâtel (4)	C	34	45	1·32
	D	58	71	1·23
Timaru, New Zealand (10)		68	86	1·26
Berne (4)	C	58	67	1·15
	D	88	89	1·01

[A = excluding very slight enlargements. B = including very slight.
C = Category III and upwards. D = Category II and upwards.]

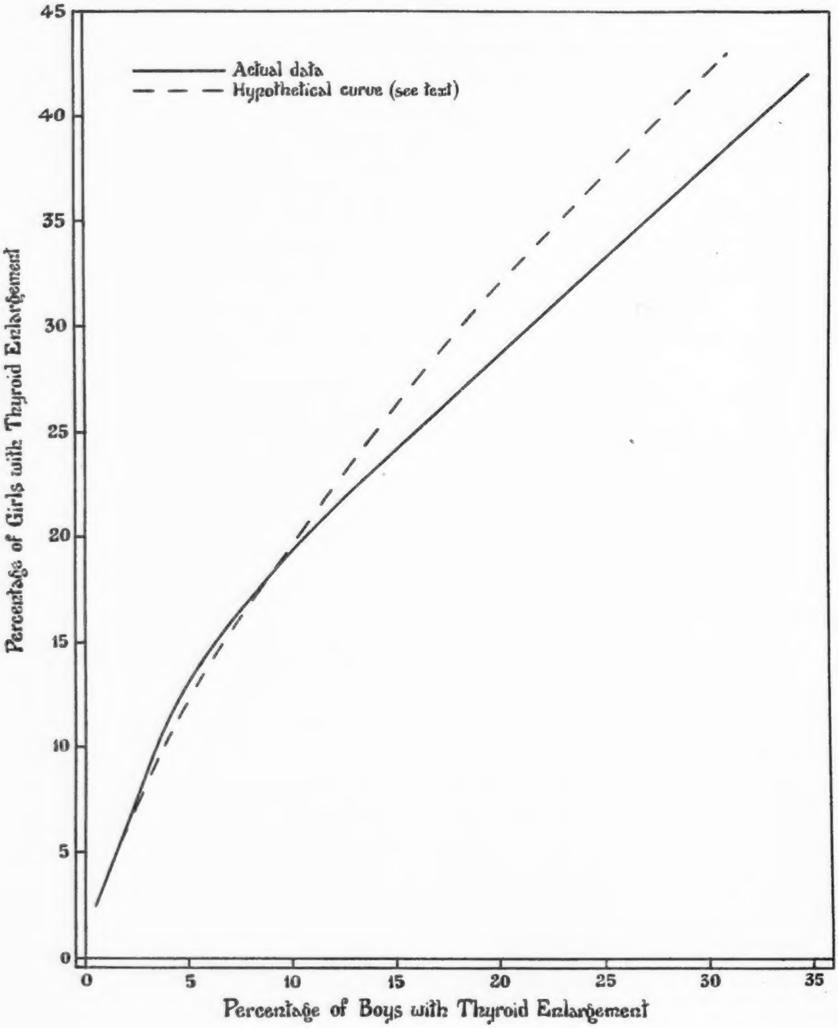

FIG. 3.

TABLE XIII.

Correlation between Rates of Thyroid Enlargement in Boys and Girls in 278 Areas of England and Wales.

GIRLS.

Percentage with Thyroid Enlargement. Central Values.

Boys. Percentage with Thyroid Enlargement. Central Values.	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	Total.
0·5	81	36	9	5	1	2	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	136
1·5	3	6	21	3	4	2	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	41
2·5	1	1	3	5	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	14
3·5	—	1	1	4	—	4	1	1	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	14
4·5	—	—	—	1	4	2	5	—	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—	14
5·5	—	—	—	1	—	6	2	3	1	1	1	1	—	—	—	—	—	—	—	—	—	—	—	16
6·5	—	—	—	—	—	—	1	—	2	—	—	—	1	—	—	—	—	—	—	—	—	—	1	5
7·5	—	—	2	—	—	2	1	1	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8
8·5	—	—	—	—	—	—	1	—	—	1	1	2	—	1	—	—	—	—	—	—	—	—	—	6
9·5	—	—	—	—	—	—	1	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	3
10·5	—	—	—	—	—	—	—	1	1	2	—	—	—	—	—	—	—	—	—	—	—	—	—	4
11·5	—	—	—	—	—	—	—	—	—	—	1	—	1	1	1	—	—	—	1	—	—	—	—	5
12·5	—	—	—	1	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	3
13·5	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
14·5	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	2
15·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
16·5	—	—	—	—	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	2
17·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
18·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
19·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	—	2
20·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1
21·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
22·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
23·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
24·5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1
Total	85	44	37	20	13	18	15	8	8	6	4	6	3	4	2	—	—	—	2	2	—	—	1	278

Standard deviations, of boys' rate 4·033 per cent., of girls' rate 8·059 per cent. $r = 0{\cdot}8204 \pm 0{\cdot}0132$.

Evidently the sex ratio approaches unity as the goitre rate becomes high. This is also supported by my own results in Table II, thus:

Bath	Rate in boys = 8·8 %	Ratio = 2·48
Torquay and Plymouth	Mean rate in boys = 17·3 %	Ratio = 1·64
Exeter, Taunton, and Okehampton	Mean rate in boys = 27·4 %	Ratio = 1·25

In Table XIII the recorded rates for girls have been correlated with the rates for boys in 278 separate areas, rural and town, of England and Wales. The resulting correlation coefficient[24] is $r = 0{\cdot}8204 \pm 0{\cdot}0132$ and η[25] $= 0{\cdot}8737$, $\eta^2 - \bar{\eta}^2 = 0{\cdot}7094$, probable error of $\bar{\eta}^2 = 0{\cdot}0129$. The regression line of prevalence in girls on prevalence in boys is not linear, but takes the form shown in Fig. 3, which has been drawn by means of a spline through the mean points after grouping several together.

TABLE XIV.

Goitre rate in boys (per cent., central values)	0·5	2·0	3·5	4·5	5·5	7·0	10·5	18·5	Total.
No. of areas	136	55	14	14	16	13	22	8	278
Mean rate in girls	2·41	6·18	10·28	12·14	14·00	15·92	20·20	27·50	—
Sex ratio	4·8	3·1	2·9	2·7	2·5	2·3	2·1	1·5	—

To carry the curve farther, my own observations in Devon suggest that at a boys' rate of 30 per cent. the girls' rate would be about 37·5, whilst the New Zealand figures suggest 40, and the American figures 45. Using my own figure, since I was using the same definition, continuing the curve through this point and thence as a straight line, it would reach the point 100 per cent. for girls at 97 per cent. for boys. This is reasonable since the curve must reach the 100 per cent. girls' rate at a point where the boys' rate is still less than 100, and the trend of the curve and the Berne figures make it unlikely that the boys' rate can be less than 95 per cent. at this point; we may therefore regard the complete curve as fairly reliable. It is not possible to say exactly what occurs at the zero end, i. e. whether a small percentage of thyroid enlargement may be present in girls without a corresponding fraction of, say, $\frac{1}{5}$ as many also occurring in boys. The indications are that 3 or 4 per cent. of girls will be found in most parts of England and Wales to exhibit enlargement of the gland according to the standard of the mean observer, though on the 42 mm. standard it would possibly be entirely absent in some localities. The fact that certain localities give rates below 1 per cent. does not disprove this, since owing to the probable error due to personal equation it will be seen presently that no single or combined area gives a rate for girls which can be said to be significantly below 3 per cent. Whether such enlargement is anywhere entirely absent in boys must also remain doubtful, but it seems probable that in some areas it may be practically absent.

In the case of any *infective* disease to which girls were very susceptible and boys not very susceptible, a fall in sex ratio would occur with increasing severity of the infective process, but this fall would not be appreciable until a large pro-

[24] The coefficient of correlation between number of boys with enlarged thyroid and number of girls with enlarged thyroid for population constant is $r = 0{\cdot}8393 \pm 0{\cdot}0114$.

[25] i. e. the correlation ratio of girls' rate on boys' rate.

portion of the population had been attacked; the regression line of girls' on boys' rates would not therefore take the form of that shown by Fig. 3, where the fall in sex ratio occurs chiefly in the first and not in the last part of the curve. The form of the curve could, however, be readily explained on the theory of iodine deprivation as the cause of thyroid enlargement, on the supposition that the average girl requires a slightly larger amount of iodine to maintain metabolism than the average boy of the same age, and that the minimal iodine requirements of individuals are distributed about these mean values according to one of the ordinary forms of frequency distribution with a rather larger dispersion for girls than boys. On this hypothesis, as the level of daily iodine supply is reduced, the girls with highest threshold of iodine requirement would be the first to suffer, and the sex ratio would be high at first; but with further reduction the tail of the boys' distribution would become increasingly involved, and the ratio would rapidly fall.[26]

(b) *Urbanization.* Both in boys and girls the thyroid rate is significantly higher in the aggregate of rural districts or 'county areas' than in the aggregate of urban districts and boroughs, and higher in the latter than in the large towns generally, the rates being:

	Boys.	*Girls.*
County areas	$3{\cdot}52 \pm 0{\cdot}27$	$9{\cdot}14 \pm 0{\cdot}43$
Urban districts and boroughs . .	$2{\cdot}79 \pm 0{\cdot}32$	$7{\cdot}19 \pm 0{\cdot}53$
County boroughs	$1{\cdot}40 \pm 0{\cdot}27$	$4{\cdot}63 \pm 0{\cdot}46$

This might be due to the areas of high prevalence containing proportionately less town population than the regions of low prevalence, owing to geological differences or from accidental causes, and in that case these figures would not indicate a direct connexion with urbanization. In the next section, division has been made between what I have termed 'goitre areas' and 'non-goitre areas', and since this division has been primarily based on the rates in rural areas, the towns involved in these geographical divisions being then necessarily included, this question can be settled by comparing the rates in the rural and urban populations within each of these separate areas. The full details are given in Table XVIII, and if reference be made to the rates in girls for the divisions numbered 1 to 7 where goitre prevalence is high, it will be seen that the rural rates are in all cases higher, and in most cases considerably higher, than in the towns; they are significantly higher than in county boroughs in 6 out of the 7 areas, and significantly higher than in the small towns in 4 out of the 7 areas. The rates in small towns are also higher than in county boroughs in 6 out of the 7 divisions, though not significantly so.

In the non-goitre divisions numbered 10 to 14, however, there are no significant differences between the rates in the three classes of area, which

[26] As an example, if the distribution of minimal iodine requirements followed the 'normal' curve, a computation shows that if the iodine requirements of girls had a standard deviation about their mean equal to 1·16 times that for boys, and their mean requirement was greater than that for boys by 0·3 times the standard deviation for boys, the sex-ratio of girls to boys who would suffer deficiency would follow the dotted curve in Fig. 3. It would be possible to obtain a better fit by postulating skew distributions instead of 'normal'.

TABLE XV.

County Areas, excluding Urban Districts and Towns with Independent Education Authority.

County.	Subdivisions, if any.	Nos. of Areas to which allotted.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. No. with Enlarged Thyroid.	Boys. Percentage recorded.	Girls. Total examined.	Girls. No. with Enlarged Thyroid.	Girls. Percentage recorded.	Boys and Girls. Mean Rate.	Altitude above Sea-level in Feet. Percentage Distribution of Area. 0–	250–	500–	1000–	Mean Altitude.	Geology.
Bedfordshire	—	12, 21	1	748	12	1·60	592	50	8·45	5·02	58	36	6	—	III	*f*
Berkshire	—	12, 21	2	967	8	0·83	877	34	3·88	2·35	48	40	12	—	III	*g*
Brecknockshire	—	6, 19	1	*317*	*13*	—	*318*	*54*	—	10·55	—	4	40	56	XII	*b*
Buckinghamshire	—	2, 20	2	356	27	7·58	375	43	11·46	9·52	22	67	11	—	IV	*g*
Cardiganshire	—	10, 15	1	327	1	0·31	352	10	2·84	1·57	7	26	40	27	IX	*a*
Carmarthenshire	—	6, 15	2	555	30	5·41	578	92	15·92	10·66	23	31	37	9	VI	*a*
Carnarvonshire	—	7, 15	2	431	15	3·48	475	52	10·95	7·21	29	24	20	27	VII	*a*
Cheshire	SW.	7, 15	1	925	93	10·05	1004	169	16·83	13·44						
	W.	7, 15	1	660	48	7·27	669	143	21·38	14·32	71	20	7	2	III	*e*
	NE.	7, 15	1	428	18	4·20	456	59	12·94	8·57						
	Mid.	11, 15	1	967	2	0·26	1268	39	3·08	1·67						
Cornwall	—	1, 16	4	1178	57	4·84	1179	201	17·05	10·95	25	35	39	1	V	*b*
Denbighshire	—	7, 15	2	567	59	10·41	696	101	14·51	12·46	18	14	36	32	IX	*a*
Derbyshire	—	4, 20	20	3592	185	5·15	3573	424	11·87	8·51	17	36	30	17	VII	*c*
Devonshire	NW.	1, 16	1	565	10	1·77	633	31	4·90	3·34	23	31	40	6	VI	*b*
	Exeter	1, 16	1	516	58	11·24	513	112	21·87	16·53	24	31	40	5	VI	*e*
	W.	1, 16	1	302	15	4·96	269	61	22·68	13·82	3	49	33	15	VII	*c*
	SE.	1, 16	1	478	99	20·71	471	185	39·27	29·99	18	44	38	—	V	*e*
	Newton	1, 16	1	251	5	1·99	269	29	10·78	6·38	31	33	26	10	VI	*b*
	SW.	1, 16	1	120	—	0·00	145	9	6·21	3·10	36	32	17	15	VI	*b*
Dorsetshire	—	14, 17	4	1087	1	0·09	977	11	1·12	0·60	51	39	10	—	III	*g*
Durham	Weardale	8, 18	1	70	13	18·57	83	29	34·94	26·75	28	31	19	22	VII	*e*
	Rest	13, 18	11	3145	139	4·42	3356	335	9·98	7·20						*d*
Essex	—	13, 18	12	2526	1	0·04	2302	19	0·82	0·43	79	21	—	—	II	*h*
Flintshire	—	10, 15	1	375	7	1·87	402	20	4·97	3·42	41	28	30	1	IV	*d*
Glamorganshire	—	10, 15	6	*3971*	15	—	*3971*	68	—	1·05	40	19	26	15	VI	*d*
Gloucestershire	W.	11, 19	3	*1062*	*13*	—	*1055*	*52*	—	3·08	76	12	11·5	0·5	III	*f*
	E.	2, 19	2	*823*	*27*	—	*832*	*98*	—	7·53	12	46	42	—	V	*f*
Hampshire	—	5, 17	9	1983	117	5·90	1920	255	13·28	11·59	50	41	9	—	III	*g*
Herefordshire	—	6, 19	1	507	26	5·13	725	171	23·58	14·35	22	45	31	2	V	*b*

Hertfordshire	—	12, 21	12	6510	14	0·21	6130	76	1·24	0·72	18	78	4	—	IV	*g*
Huntingdonshire	—	12, 21	2	406	—	0·00	364	6	1·65	0·83	100	—	—	—	II	*f*
Kent	SW.	9, 17	1	627	53	8·45	589	165	28·01	18·23	68	26	6	—	III	*g*
	Rest	14, 17	2	2104	4	0·19	2539	56	2·21	1·20						
Lancashire	N.	10, 15	3	570	4	0·70	520	12	2·31	1·50	59	20	14	7	IV	*c*
	Pennine	4, 15	5	864	93	10·76	846	169	19·97	15·36	26	23	40	11	VI	*d*
	S. (part)	10, 15	7	1120	52	4·64	923	104	11·27	7·95	77	20	3	—	II	*e*
	S. (part)	7, 15	2	584	52	8·90	490	86	17·55	13·22						
Leicestershire	—	3, 20	3	1690	51	3·02	1721	230	13·36	8·19	18	73	9	—	IV	*f*
Lincolnshire	Holland	13, 18	2	*684*	*3*	—	*683*	*8*	—	0·80	100	—	—	—	II	*h*
	Kesteven	13, 18	1	*292*	*10*	—	*293*	*32*	—	7·18	81	19	—	—	II	*f*
	Lindsey	13, 18	7	1303	17	1·30	1354	37	2·73	2·01	89	11	—	—	II	*g*
Merionethshire	—	7, 15	1	304	16	5·26	267	38	14·23	9·74	7	10	29	54	XI	*a*
Middlesex	—	12, 21	7	1928	30	1·56	1993	69	3·46	2·51	87	13	—	—	II	*h*
Monmouthshire	—	11, 19	7	2294	25	1·09	1656	50	3·02	2·05	43	20	25	12	V	*b*
Norfolk	—	13, 18	5	*1766*	*33*	—	*1766*	*104*	—	3·88	99	1	—	—	II	*g*
Northamptonshire	—	3, 20	2	1001	42	4·20	1024	105	10·26	7·23	22	68	10	—	IV	*f*
Northumberland	W.	8, 18	2	450	44	9·78	419	106	25·20	17·53	26	23	33	18	VII	*c*
	E.	13, 18	5	1878	50	2·67	1626	116	7·13	4·90						*d*
Nottinghamshire	NE.	13, 20	1	295	3	1·02	256	15	5·86	3·44	77	20	3	—	II	*e*
	Rest	4, 20	3	1194	67	5·59	1146	172	15·01	10·30						
Oxfordshire	—	2, 20	17	650	74	11·39	634	236	37·22	24·30	28	60	12	—	IV	*f*
Pembrokeshire	—	10, 15	2	2615	1	0·04	2392	19	0·79	0·42	52	30	16	2	IV	*a*
Peterborough	Soke of	3, 20	1	*160*	*10*	—	*161*	*30*	—	12·46	100	—	—	—	II	*h*
Radnorshire	—	11, 19	1	117	4	3·42	107	7	6·55	4·98	—	4	47	49	XII	*b*
Rutland	—	3, 20	1	*388*	56	—	*388*	106	—	20·87	33	63	4	—	IV	*f*
Shropshire	—	11, 19	5	1766	27	1·53	1867	88	4·61	3·07	19	51	25	5	V	*a*
Somersetshire	Weston	1, 16	1	464	13	2·80	424	17	4·01	3·40	100	—	—	—	II	*e*
	NE.	1, 16	1	1558	69	4·43	1578	192	12·16	8·30	35	58	7	—	IV	*e*
	NW.	1, 16	1	1728	192	11·11	1698	432	25·15	18·13	75	5	18·7	0·3	III	*e*
	SE.	1, 16	1	1158	226	19·52	1338	384	28·70	24·11	60	29	11	—	III	*e*
	W.	1, 16	1	908	606	66·74	885	683	77·18	71·96	29	19	29	23	VII	*b*
Surrey	—	12, 21	12	3324	111	2·56	3045	300	9·85	6·20	58	32	10	—	III	*g*
Sussex East	W.	9, 17	1	*409*	22	—	*410*	48	—	8·55	72	24	4	—	III	*g*
	E.	14, 17	1	*415*	7	—	*415*	18	—	3·01						
Sussex West	—	14, 17	3	*906*	*13*	—	*905*	*26*	—	2·15	77	20	3	—	II	*g*
Warwickshire	—	11, 19	5	1949	19	0·97	1916	80	4·17	2·57	18	77	5	—	IV	*e*
Wight, Isle of	—	5, 17	2	847	161	19·01	845	308	36·45	27·73	80	16	4	—	II	*g*
Wiltshire	—	2, 20	5	*677*	*61*	—	*677*	*180*	—	17·65	17	60	23	—	V	*g*
Worcestershire	—	6, 19	9	*1976*	*73*	—	*1976*	*289*	—	9·16	66	25	9	—	III	*e*
Yorks, E. Riding	—	13, 18	2	1490	76	5·10	1440	172	11·94	8·52	80	15	5	—	II	*g*
N. Riding	—	13, 18	5	2095	28	1·34	1959	77	3·93	2·63	41	13	27	19	III	*f*
W. Riding	Pennine	4, 20	2	*324*	*14*	—	*325*	*28*	—	6·47	37	21	26	16	VI	*d*
	Rest	13, 20	4	*1215*	*27*	—	*1215*	*52*	—	3·25						

average 4–5 per cent. for girls. It appears likely, therefore, that urbanization has no appreciable effect on the ordinary prevalence of small enlargements and sporadic goitres, but that the local factors which go to intensify the prevalence of such enlargements and to make goitre 'endemic' are much more pronounced in rural districts than small towns, and in small than large towns.

Geographical Distribution of Thyroid Enlargement at Age 12.

The results of the school medical officers' survey of children aged 12 are set out in detail in Tables XV to XVIII. Table XV relates to the areas controlled by the education authorities of the County Councils, which are for the most part rural in character, but include many small townships which have no independent education authority. The geographical unit is here the administrative county; thus certain of the geographical counties (Lincolnshire, Sussex) are divided into two or more separate administrative divisions. In certain other cases separate returns have been obtained both for boys and girls, relating to the subdivisions of the county areas allotted to individual medical officers, and where the boundaries are known, and some useful purpose is served by stating them separately, these counties have been subdivided in the table (Cheshire, Devonshire, Durham, Gloucestershire, Kent, Lancashire, Northumberland, Nottingham, Somerset, Sussex East, West Riding). The counties from which returns were available have been arranged alphabetically. The numbers in the third column relate to the geographical divisions of Table XVIII, and show to which of these divisions each particular area has been allotted. Next is given the number of medical officers who took part in the survey, this being important for the computation of the probable errors. All the thyroid rates are stated as percentages. In three counties (Glamorgan, Sussex East, Rutland) the total children examined were recorded and also the number of boys and girls with enlarged thyroid; here I have assumed that the totals examined consisted of boys and girls in equal numbers. In eight other areas (Norfolk, Holland, Kesteven, Sussex West, Worcestershire, Wiltshire, Brecknockshire, Soke of Peterborough) boys and girls were not separately recorded; in these cases I have assumed that boys and girls were examined in equal numbers and that the sex ratio was the same as for the rest of the geographical division to which the area was allocated (i.e. Nos. 15–21 in Table XVIII). For the West Riding a similar adjustment was required for the subdivisions on the basis of the sex ratio for the county, which was known.

All figures so adjusted have been entered in italics in the tables, and the individual rates for boys and girls have then not been calculated; in all these cases the sum of the figures in italics is the total which was recorded for 'children'. The 'mean rates' are the arithmetic means of the boys' and girls' rates in all cases; in the areas just referred to these would be identical with the recorded rates in 'children'.

TABLE XVI.

Municipal Boroughs and Urban Districts with Independent Education Authority.

County.	Urban District or Municipal Borough.	Place.	Nos. of Areas to which allotted.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. No. with Enlarged Thyroid.	Boys. Percentage recorded.	Girls. Total examined.	Girls. No. with Enlarged Thyroid.	Girls. Percentage recorded.	Boys and Girls. Mean Rate.	Sea-coast or Inland.	Altitude. Group.	Altitude. Miles Distant from Contour Lines. 250 ft.	500 ft.	1,000 ft.
Bedfordshire	B	Luton	12, 21	1	441	2	0·45	421	29	6·90	3·67	I	C	—	1	68
Berkshire	B	Maidenhead	12, 21	1	112	—	—	122	1	0·82	0·41	I	B	6	8	62
	B	Newbury	12, 21	1	56	—	—	66	6	3·39	1·69	I	B	1	6	48
	B	New Windsor	12, 21	1	435	—	—	448	3	0·67	0·33	I	B	3	12	67
Buckinghamshire	B	Chepping Wycombe	2, 20	1	172	12	6·97	143	35	24·48	15·72	I	C	—	1	58
Carmarthen	B	Carmarthen	6, 15	1	83	2	—	83	28	—	18·07	I	A	1	3	7
	B	Llanelly	6, 15	1	253	1	0·39	233	6	2·58	1·44	I	A	1	2	18
Cheshire	B	Congleton	7, 15	1	157	3	1·91	98	22	22·40	12·15	I	C	—	2	4
	B	Crewe	7, 15	1	288	21	7·29	295	50	16·27	11·78	I	B	3	6	13
	B	Hyde	4, 15	1	210	18	8·57	231	32	13·85	11·21	I	C	—	1	3
	B	Stalybridge	4, 15	1	75	12	16·00	74	11	14·87	15·44	I	C	—	1	2
Cornwall	B	Penzance	1, 16	1	86	—	—	34	—	—	—	S	A	1	2	56
Cumberland	B	Workington	10, 15	1	203	5	2·46	199	2	1·00	1·73	S	A	1	4	8
Denbighshire	B	Wrexham	7, 15	2	178	24	13·48	166	9	5·42	9·45	I	C	—	2	4
Derbyshire	B	Chesterfield	4, 20	1	388	6	1·54	353	19	5·38	3·46	I	C	—	2	4
	B	Glossop	4, 20	1	98	5	5·10	129	15	11·63	8·36	I	D	—	—	2
	B	Ilkeston	4, 20	1	467	60	12·85	586	122	20·82	16·94	I	B	1	6	14
Devonshire	B	Barnstaple	1, 16	1	69	1	1·45	90	11	12·20	6·82	S	A	1	2	6
	B	Tiverton	1, 16	1	64	4	6·25	68	30	44·12	25·18	I	B	1	1	12
	B	Torquay	1, 16	1	195	2	1·03	206	8	3·88	2·45	S	A	1	6	11
Dorsetshire	B	Poole	14, 17	1	277	25	9·03	270	34	12·60	10·81	S	A	3	14	61
	B	Weymouth	14, 17	1	132	5	3·78	108	11	10·19	6·98	S	A	3	5	52

TABLE XVI (*continued*).

County.	Urban District or Municipal Borough	Place.	Nos. of Areas to which allotted.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. No. with Enlarged Thyroid.	Boys. Percentage recorded.	Girls. Total examined.	Girls. No. with Enlarged Thyroid.	Girls. Percentage recorded.	Boys and Girls. Mean Rate.	Sea-coast or Inland.	Altitude. Group.	Altitude. Miles distant from Contour Lines. 250 ft.	Altitude. Miles distant from Contour Lines. 500 ft.	Altitude. Miles distant from Contour Lines. 1,000 ft
Durham	U D	Felling	13, 18	1	301	—	—	325	5	1·54	0·77	I	C	—	1	15
	B	Hartlepool	13, 18	1	287	3	1·04	339	5	1·48	1·26	S	A	3	19	27
	U D	Hebburn	13, 18	1	191	23	12·04	217	15	6·91	9·48	I	A	2	3	17
	B	Jarrow	13, 18	1	393	—	—	369	6	1·63	0·81	I	C	4	5	19
	B	Stockton-on-Tees	13, 18	1	420	2	0·47	326	9	2·76	1·61	I	A	5	7	23
Essex	U D	Barking	13, 18	1	206	3	1·46	217	9	4·15	2·81	I	B	9	18	97
	B	Chelmsford	13, 18	1	129	—	—	171	1	0·58	0·29	I	B	3	41	>100
	B	Colchester	13, 18	1	*195*	—	—	*195*	2	—	0·51	I	B	12	52	>100
	B	Harwich	13, 18	1	94	—	—	100	—	—		S	A	19	67	>100
	U D	Ilford	13, 18	2	626	21	3·35	622	105	16·89	10·12	I	B	9	29	97
	U D	Leyton	13, 18	3	911	2	0·21	984	36	3·66	1·94	I	B	6	25	90
Glamorganshire	U D	Aberdare	10, 15	1	456	42	9·21	416	93	22·36	15·94	I	D	—	—	1
	U D	Pontypridd	10, 15	1	336	18	5·96	302	33	10·93	8·45	I	C	—	1	2
	B	Port Talbot	10, 15	1	384	2	0·50	350	10	2·86	1·68	S	A	1	2	3
	U D	Rhondda	10, 15	3	1621	21	1·29	1557	151	9·69	5·46	I	D	—	—	1
Gloucestershire	B	Cheltenham	11, 19	1	782	4	0·51	870	12	1·38	0·95	I	C	—	2	3
Hampshire	B	Aldershot	5, 17	1	169	—	—	183	9	4·92	2·46	I	C	—	1	68
	B	Winchester	5, 17	1	120	5	4·17	110	14	12·73	8·45	I	A	1	2	63
Herefordshire	B	Hereford	6, 19	1	151	25	16·56	135	35	25·93	21·25	I	B	2	3	15
Hertfordshire	B	Hemel Hempstead	12, 21	1	114	5	4·39	107	9	9·35	6·87	I	C	—	1	66
Kent	U D	Beckenham	14, 17	1	181	—	—	141	2	1·42	0·71	I	B	2	3	90
	B	Bromley	14, 17	1	209	1	0·48	184	2	1·09	0·78	I	A	1	5	96
	B	Chatham	14, 17	1	380	—	—	415	2	0·48	0·24	I	A	2	3	>100
	B	Dover	14, 17	1	250	—	—	224	3	1·34	0·67	S	A	1	4	>100
	U D	Erith	14, 17	1	276	—	—	303	3	0·99	0·50	I	A	6	8	>100
	B	Faversham	14, 17	1	68	—	—	75	3	4·00	2·00	I	B	2	6	>100
	B	Folkestone	14, 17	1	172	—	—	172	2	1·16	0·58	S	A	1	1	>100

	B	Gravesend	14, 17	1	*726*	—	—	*727*	7	—	0·48	I	A	2	5	>100
	B	Maidstone	14, 17	1	207	1	0·48	227	35	15·42	7·95	I	B	1	2	>100
	B	Margate	14, 17	1	191	—	—	209	1	0·48	0·24	S	A	14	21	>100
	U D	Penge	14, 17	1	156	9	5·77	140	15	10·71	8·24	I	B	2	3	90
	B	Ramsgate	14, 17	1	204	—	—	247	—	—	—	S	A	12	19	>100
	B	Rochester	14, 17	1	226	—	—	251	—	—	—	I	A	1	3	>100
	B	Tunbridge Wells	9, 17	1	461	37	8·03	514	99	19·26	13·64	I	C	—	2	>100
Lancashire	B	Accrington	4, 15	1	212	—	—	223	4	1·80	0·90	I	D	—	—	2
	B	Ashton-under-Lyne	4, 15	1	223	8	3·59	227	24	10·57	7·08	I	C	—	2	3
	B	Bacup	4, 15	1	162	1	0·62	182	3	1·65	1·13	I	D	—	—	1
	U D	Chadderton	4, 15	1	437	31	7·09	443	57	12·87	9·98	I	C	—	3	6
	B	Chorley	4, 15	1	188	—	—	207	5	2·41	1·20	I	C	—	1	3
	B	Clitheroe	10, 15	1	204	12	5·88	161	25	15·43	10·65	I	B	1	2	3
	B	Colne	4, 15	1	*666*	48	—	*667*	103	—	11·25	I	D	—	—	2
	B	Darwen	4, 15	1	263	37	14·07	242	45	18·59	16·33	I	D	—	—	1
	B	Eccles	10, 15	1	295	5	1·69	313	16	5·11	3·40	I	B	2	8	10
	U D	Farnworth	10, 15	1	*182*	*5*	—	*183*	*9*	—	3·84	I	C	—	3	5
	U D	Hindley	10, 15	1	239	29	12·13	273	38	13·92	13·01	I	B	1	4	5
	B	Heywood	10, 15	1	119	4	3·36	159	19	11·95	7·65	I	C	—	1	4
	B	Lancaster	10, 15	1	238	9	3·78	253	16	6·32	5·05	I	A	1	3	4
	B	Leigh	10, 15	1	431	3	0·70	449	11	2·45	1·57	I	B	3	6	8
	B	Middleton	10, 15	1	*959*	17	—	*959*	39	—	2·92	I	C	—	3	6
	B	Morecambe	10, 15	1	233	1	0·43	240	2	0·83	0·63	S	A	4	6	8
	B	Mossley	4, 15	1	107	—	—	79	3	3·79	1·90	I	D	—	—	1
	U D	Radcliffe	10, 15	1	135	—	—	161	—	—	—	I	B	1	2	5
	B	Rawtenstall	4, 15	1	*172*	—	—	*173*	6	—	1·74	I	D	—	—	1
	U D	Stretford	10, 15	1	112	2	1·78	220	7	3·19	2·48	I	B	8	11	13
	U D	Swinton	10, 15	1	251	13	5·18	288	37	12·84	9·01	I	B	1	6	10
	U D	Waterloo and Seaforth	10, 15	1	630	5	0·79	602	19	3·15	1·97	S	A	12	22	23
Leicestershire	B	Loughborough	3, 20	1	107	—	—	59	1	1·69	0·84	I	B	2	3	28
Lincolnshire, Holland	B	Boston	13, 18	1	65	—	—	73	—	—	—	I	A	13	32	64
Middlesex	B	Acton	12, 21	2	504	3	0·59	490	25	5·10	2·84	I	B	8	13	78
	U D	Chiswick	12, 21	1	337	—	—	207	8	3·87	1·94	I	B	9	12	78
	B	Ealing	12, 21	1	543	5	0·92	500	14	2·80	1·86	I	B	7	14	80
	U D	Edmonton	12, 21	2	593	28	4·72	609	58	9·55	7·14	I	B	4	20	90
	U D	Enfield	12, 21	1	290	—	—	240	1	0·41	0·21	I	B	3	19	88
	U D	Hendon	12, 21	1	224	1	0·45	241	25	10·37	5·41	I	B	2	12	86
	U D	Heston and Isleworth	12, 21	1	379	1	0·26	294	9	3·06	1·66	I	B	8	17	67
	B	Hornsey	12, 21	1	342	1	0·29	296	—	—	0·15	I	B	5	16	88

TABLE XVI (*continued*).

County.	Urban District or Municipal Borough.	Place.	Nos. of Areas to which allotted.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. No. with Enlarged Thyroid.	Boys. Percentage recorded.	Girls. Total examined.	Girls. No. with Enlarged Thyroid.	Girls. Percentage recorded.	Boys and Girls. Mean Rate.	Sea-coast or Inland.	Altitude. Group.	Miles distant from Contour Lines. 250 ft.	500 ft.	1,000 ft.
	U D	Tottenham	12, 21	3	687	1	0·15	817	11	1·34	0·75	I	B	6	20	90
	U D	Twickenham	12, 21	1	254	—	—	186	—	—	—	I	B	8	10	80
	U D	Willesden	12, 21	6	717	1	0·14	591	9	1·52	0·83	I	B	6	16	83
Monmouthshire	U D	Abertillery	11, 19	1	157	1	0·64	148	7	4·73	2·68	I	C	—	1	14
	U D	Ebbw Vale	11, 19	1	723	175	24·20	693	267	38·53	31·36	I	D	—	—	1
Northamptonshire	U D	Kettering	3, 20	1	148	1	0·68	146	15	10·27	5·47	I	B	1	5	63
Northumberland	B	Blyth	13, 18	1	124	1	0·81	131	5	3·82	2·31	S	A	7	11	20
	B	Wallsend	13, 18	1	336	3	0·89	331	4	1·21	1·05	I	A	3	4	27
Nottinghamshire	B	Mansfield	4, 20	1	379	38	10·03	391	71	18·15	14·09	I	C	—	1	14
Oxfordshire	B	Banbury	2, 20	1	103	2	1·94	111	8	7·21	4·57	I	C	—	2	28
Pembrokeshire	B	Pembroke	10, 15	1	74	—	—	90	3	3·33	1·66	S	A	6	11	19
Peterborough Soke	B	Peterborough	3, 20	1	199	—	—	218	3	1·38	0·69	I	B	10	20	63
Shropshire	B	Shrewsbury	11, 19	1	217	5	2·30	199	18	9·03	5·66	I	B	1	6	10
Somersetshire	B	Bridgwater	1, 16	1	80	—	—	114	8	7·02	3·51	I	A	2	4	9
	B	Taunton	1, 16	1	*147*	*1*	—	*147*	*7*	—	2·72	I	B	2	3	7
	B	Yeovil	1, 16	1	80	—	—	116	—	—	—	I	B	1	5	29
Staffordshire	U D	Bilston	11, 19	1	352	1	0·28	260	4	1·54	0·91	I	C	—	2	22
	U D	Cannock	11, 19	1	313	6	1·92	357	32	8·97	5·44	I	C	—	1	25
	U D	Coseley	11, 19	1	230	4	1·73	221	17	7·69	4·71	I	C	—	1	22
	B	Newcastle-under-Lyne	11, 19	1	131	—	—	118	4	3·39	1·70	I	C	—	1	11
	U D	Rowley Regis	11, 19	1	498	23	4·62	528	69	13·07	8·85	I	C	—	1	23
	B	Wednesbury	11, 19	1	*872*	—	—	*872*	5	—	0·28	I	C	—	3	30
	U D	Wolstanton	11, 19	1	290	—	—	225	4	1·78	0·89	I	C	—	1	13
Suffolk	B	Lowestoft	13, 18	1	409	22	5·35	382	67	17·54	11·45	S	A	42	94	>100

Surrey	B	Guildford	12, 21	1	*140*	—	—	*140*	—	—	—	I	B	1	2	80
	B	Kingston-on-Thames	12, 21	1	254	—	—	278	6	2·16	1·08	I	B	5	6	82
	B	Richmond	12, 21	1	111	—	—	117	—	—	—	I	B	8	10	80
Sussex East	B	Bexhill	14, 17	1	85	—	—	73	7	9·59	4·80	S	A	5	12	>100
	B	Hove	14, 17	1	*107*	—	—	*108*	*2*	—	0·93	S	A	2	3	>100
Sussex West	B	Worthing	14, 17	1	184	1	0.54	168	11	6·55	3·55	S	A	4	5	>100
Warwickshire	B	Leamington	11, 19	1	493	1	0·20	553	19	3·44	1·82	I	B	1	11	32
	B	Nuneaton	11, 19	1	*263*	*10*	—	*263*	*41*	—	9·69	I	C	—	4	47
	B	Sutton Coldfield	11, 19	1	55	—	—	64	5	7·81	3·90	I	C	—	1	32
Isle of Wight	B	Newport	5, 17	1	*63*	—	—	*63*	1	—	0·79	I	A	1	2	90
Wiltshire	B	Salisbury	2, 20	1	409	—	—	429	1	0·23	0·12	I	B	1	5	55
	B	Swindon	2, 20	1	157	13	8·28	236	55	23·30	15·79	I	C	—	2	24
Worcestershire	B	Kidderminster	6, 19	1	204	13	6·37	188	32	17·02	11·70	I	B	1	6	14
	U D	Oldbury	6, 19	1	333	1	0·30	354	19	5·37	2·84	I	C	—	2	24
Yorkshire, E. Riding	B	Beverley	13, 18	1	150	—	—	139	2	1·44	0·72	I	B	3	13	40
	B	Bridlington	13, 18	1	*126*	—	—	*126*	—	—	—	S	A	2	12	33
Yorkshire, N. Riding	B	Scarborough	13, 18	1	260	20	7·69	246	14	5·69	6·69	S	A	1	2	18
Yorkshire, W. Riding	B	Batley	13, 20	1	228	9	3·95	251	5	2·00	2·97	I	C	—	2	9
	B	Doncaster	13, 20	1	428	2	0·47	498	19	3·82	2·14	I	B	3	14	17
	B	Harrogate	13, 20	1	171	11	6·49	168	27	16·07	11·28	I	C	—	1	8
	B	Keighley	4, 20	1	247	3	1·21	277	16	5·77	3·49	I	C	—	1	3
	B	Morley	13, 20	1	163	2	1·23	150	8	5·33	3·28	I	C	—	1	9
	U D	Shipley	13, 20	1	179	8	4·47	171	12	7·02	5·75	I	C	—	1	3
	U D	Spenborough	13, 20	1	*241*	—	—	*241*	—	—	—	I	C	—	2	8
	B	Todmorden	4, 20	1	678	11	1·62	641	32	4·99	3·30	I	D	—	—	1

TABLE XVII.

County Boroughs.

County.	County Borough.	Nos. of Areas to which allocated.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. No. with Enlarged Thyroid.	Boys. Percentage recorded.	Girls. Total examined.	Girls. No. with Enlarged Thyroid.	Girls. Percentage recorded.	Boys and Girls. Mean Rate.	Sea-coast or Inland.	Altitude. Group.	Altitude. Miles distant from Contour Lines. 250 ft.	Altitude. Miles distant from Contour Lines. 500 ft.	Altitude. Miles distant from Contour Lines. 1,000 ft.
Berkshire	Reading	12, 21	2	413	9	2·18	551	34	6·17	4·18	I	B	2	6	56
Cheshire	Birkenhead	10, 15	3	1246	3	0·24	1350	9	0·67	0·45	I	B	5	13	17
	Chester	7, 15	1	328	28	8·54	269	62	23·05	15·80	I	B	5	9	13
	Stockport	7, 15	2	1074	9	0·84	1074	28	2·61	1·72	I	B	1	4	7
	Wallasey	7, 15	1	364	41	11·27	335	91	27·16	19·22	S	A	6	13	19
Cumberland	Carlisle	10, 15	1	549	2	0·35	531	17	2·86	1·60	I	B	3	6	11
Derbyshire	Derby	4, 20	1	991	23	2·32	940	66	7·02	4·67	I	B	1	6	12
Devonshire	Exeter	1, 16	1	473	2	0·42	363	4	1·10	0·76	I	A	1	3	9
	Plymouth	1, 16	2	496	26	5·24	669	61	9·12	7·18	S	A	1	5	9
Durham	Darlington	13, 18	3	465	17	3·66	404	32	7·92	5·79	I	B	3	7	12
	South Shields	13, 18	2	507	—	—	440	9	2·05	1·03	S	A	5	8	23
	Sunderland	13, 18	1	110	2	1·82	489	24	4·96	3·39	S	A	2	8	22
	West Hartlepool	13, 18	2	563	1	0·18	433	—	—	0·09	S	A	3	9	13
Essex	East Ham	13, 18	3	1307	4	0·31	1105	5	0·45	0·38	I	A	7	12	94
	Southend	13, 18	2	622	—	—	588	2	0·34	0·17	S	A	14	17	>100
	West Ham	13, 18	6	2480	4	0·16	2371	30	1·26	0·71	I	A	7	12	92
Glamorganshire	Cardiff	10, 15	4	1415	18	1·27	1457	87	5·97	3·62	S	A	3	5	15
	Merthyr Tydvil	10, 15	2	1041	34	3·27	837	42	5·02	4·14	I	D	—	—	4
Gloucestershire	Bristol	11, 19	6	2248	100	4·45	2054	201	9·78	7·12	I	B	2	5	12
	Gloucester	11, 19	1	291	7	2·41	275	6	2·18	2·30	I	B	3	4	11
Hampshire	Portsmouth	5, 17	2	1472	1	0·07	1585	6	0·38	0·22	S	A	9	12	88
	Southampton	5, 17	5	1147	10	0·87	1083	35	3·23	2·05	S	A	9	12	72
Kent	Canterbury	14, 17	1	120	1	0·83	127	6	4·72	2·77	I	B	3	8	>100

Lancashire	Barrow-in-Furness	10, 15	1	354	1	0·28	325	3	0·92	0·60	S	A	2	6	18
	Blackburn	4, 15	2	837	9	1·07	1135	64	5·64	3·35	I	C	—	1	3
	Blackpool	10, 15	1	345	19	5·51	328	64	19·51	12·51	S	A	15	16	18
	Bolton	10, 15	2	1590	5	0·31	1332	11	0·83	0·57	I	C	—	1	3
	Bootle	10, 15	1	578	4	0·69	642	80	12·46	6·57	S	A	8	16	20
	Burnley	4, 15	1	632	2	0·32	607	10	1·65	0·98	I	C	—	1	2
	Bury	10, 15	1	343	2	0·58	326	8	2·45	1·51	I	B	1	2	3
	Liverpool	10, 15	14	4914	19	0·39	4679	70	1·49	0·94	S	A	6	14	19
	Manchester	7, 15	14	3225	111	3·44	3298	520	15·77	9·60	I	B	3	7	10
	Preston	10, 15	1	958	85	8·87	923	240	26·00	17·44	I	A	5	8	10
	Rochdale	4, 15	1	707	34	4·81	749	94	12·55	8·68	I	C	—	1	3
	St. Helens	10, 15	3	689	3	0·43	636	9	1·42	0·93	I	B	6	17	18
	Salford	10, 15	3	1540	24	1·56	1310	69	5·27	3·42	I	B	3	10	11
	Southport	10, 15	1	229	1	0·44	211	3	1·42	0·93	S	A	11	17	20
	Warrington	10, 15	2	813	6	0·74	774	11	1·42	1·08	I	B	3	15	16
	Wigan	10, 15	2	540	1	0·18	535	26	4·86	2·52	I	B	1	5	7
Leicestershire	Leicester	3, 20	4	1768	36	2·04	1689	120	7·11	4·57	I	B	1	6	60
Lincolnshire,	Grimsby	13, 18	3	754	1	0·13	904	10	1·11	0·62	S	A	6	12	61
Lindsey	Lincoln	13, 18	1	192	1	0·52	71	2	2·82	1·67	I	B	16	28	42
Monmouthshire	Newport	11, 19	2	850	1	0·12	771	22	2·85	1·48	S	A	2	3	4
Norfolk	Great Yarmouth	13, 18	1	289	—	—	248	4	1·61	0·80	S	A	30	75	>100
	Norwich	13, 18	4	687	2	0·29	628	12	1·91	1·10	I	B	17	87	>100
Northamptonshire	Northampton	3, 20	1	430	1	0·23	417	2	0·48	0·35	I	B	1	8	48
Northumberland	Newcastle-on-Tyne	13, 18	4	3119	3	0·10	2964	46	1·55	0·82	S	A	1	3	15
	Tynemouth	13, 18	1	546	—	—	576	2	0·35	0·17	S	A	5	9	23
Oxfordshire	Oxford	2, 20	1	359	4	1·11	392	20	5·10	3·10	I	B	1	2	35
Somersetshire	Bath	1, 16	1	447	10	2·24	422	31	7·35	4·79	I	B	1	2	18
Staffordshire	Burton-on-Trent	11, 19	1	355	4	1·13	360	40	11·11	6·12	I	B	1	6	17
	Smethwick	11, 19	1	377	13	3·45	194	37	19·07	11·26	I	C	—	3	35
	Stoke	11, 19	3	*2477*	44	—	*2478*	117	—	3·25	I	C	—	2	8
	Walsall	11, 19	2	1035	47	4·54	960	80	8·33	6·43	I	C	—	1	26
	Wolverhampton	11, 19	2	819	1	0·12	922	16	0·17	0·14	I	C	—	1	20
Suffolk East	Ipswich	13, 18	2	677	9	1·33	609	11	1·86	1·60	I	A	10	63	>100
Surrey	Croydon	12, 21	3	488	10	2·05	619	34	5·49	3·77	I	B	1	2	88
Sussex East	Brighton	14, 17	2	612	4	0·65	616	14	2·27	1·46	S	A	1	2	>100
	Hastings	9, 17	1	192	15	7·81	182	32	17·58	12·70	S	A	1	20	>100
Warwickshire	Birmingham	11, 19	8	*1707*	*58*	—	*1708*	*158*	—	6·32	I	C	—	2	28
	Coventry	11, 19	2	573	2	0·35	594	17	2·86	1·60	I	C	—	6	40

TABLE XVII (*continued*).

County.	County Borough.	Nos. of Areas to which allocated.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. No. with Enlarged Thyroid.	Boys. Percentage recorded.	Girls. Total examined.	Girls. No. with Enlarged Thyroid.	Girls. Percentage recorded.	Boys and Girls. Mean Rate.	Sea-coast or Inland.	Group.	Altitude. Miles distant from Contour Lines. 250 ft.	500 ft.	1,000 ft.
Worcestershire	Dudley	6, 19	2	1823	1	0·05	1661	17	1·02	0·54	I	D	—	—	22
	Worcester	6, 19	1	347	4	1·15	322	11	3·41	2·28	I	B	6	7	17
Yorkshire	York	13, 18	2	535	1	0·19	485	15	3·09	1·64	I	B	12	13	28
" E. Riding	Kingston-on-Hull	13, 18	7	2273	6	0·26	1830	8	0·44	0·35	S	A	6	8	54
" N. Riding	Middlesbrough	13, 18	2	1063	—	—	1231	3	0·24	0·12	S	A	4	5	12
" W. Riding	Barnsley	13, 20	1	396	4	1·01	446	2	0·45	0·73	I	B	1	3	9
	Bradford	13, 20	5	891	7	0·79	1005	24	2·38	1·58	I	C	—	1	3
	Halifax	13, 20	2	444	—	—	360	4	1·11	0·56	I	D	—	—	1
	Huddersfield	13, 20	1	395	—	—	497	7	1·41	0·71	I	C	—	1	5
	Leeds	13, 20	8	2098	8	0·38	2160	43	1·99	1·18	I	B	1	4	12
	Rotherham	13, 20	1	586	3	0·51	505	7	1·38	0·95	I	B	1	4	10
	Sheffield	13, 20	7	2012	20	0·99	2302	103	4·47	2·73	I	C	—	1	4
	Wakefield	13, 20	1	1225	2	0·16	1179	5	0·42	0·29	I	B	1	6	12

Key No. of Area.	Definition of Areas based upon (*a*) Goitre prevalence, (*b*) Geographical position.	County Council Areas (chiefl				
		No. of M.O.'s taking part.	Boys.			
			Total examined.	Enlargement of Thyroid.		Total examined.
				No.	%.	
	(a) ***Areas of high prevalence—***					
1	South-western Counties	15	4568	470	$10·29 \pm 1·38$	4817
2	South Midland area	26	2506	189	$7·54 \pm 0·97$	2518
3	East Central area	7	3239	159	$4·91 \pm 1·71$	3294
4	South Pennine area	30	5974	359	$6·01 \pm 0·86$	5890
1–4	Total 'goitre belt'	78	16287	1177	$7·23 \pm 0·55$	16519
5	Hampshire and Isle of Wight	11	2830	278	$9·83 \pm 1·59$	2765
6	Worcester to Carmarthen	13	3355	142	$4·23 \pm 1·24$	3597
7	Cheshire to Carnarvon	10	3899	301	$7·72 \pm 1·57$	4047
8	W. Northumberland and Weardale	3	520	57	$10·96 \pm 3·15$	502
9	SW. Kent and part of Sussex	2	1036	75	$7·24 \pm 3·46$	999
5–9	Total subsidiary areas	39	11640	853	$7·33 \pm 0·79$	11910
1–9	Total areas of high prevalence	117	27927	2030	$7·28 \pm 0·45$	28429
	Areas of low prevalence—					
10	Western Seaboard area	20	8978	80	$0·89 \pm 0·89$	8570
11	W. Midlands and Central Wales	22	6779	73	$1·08 \pm 0·85$	6547
12	East and SE. Midlands	36	13883	175	$1·26 \pm 0·67$	13001
13	East Seaboard and West Riding	55	16689	387	$2·33 \pm 0·56$	16250
14	Southern Seaboard area	10	4512	27	$0·60 \pm 1·24$	4836
10–14	Total areas of low prevalence	143	50841	742	$1·46 \pm 0·34$	49204
	(b) ***Geographical Divisions—***					
15	West Seaboard Counties	38	15263	506	$3·31 \pm 0·70$	15309
16	South-western Counties	15	4568	470	$10·29 \pm 1·38$	4817
17	South Seaboard Counties	23	8378	380	$4·53 \pm 0·94$	8600
18	Eastern Seaboard Counties	53	15699	414	$2·64 \pm 0·58$	15281
	Total Seaboard Counties	129	43908	1770	$4·03 \pm 0·39$	44007
19	W. Midland and Border Counties	34	9435	210	$2·23 \pm 0·71$	9130
20	E. Central and S. Midland Counties	61	11542	617	$5·34 \pm 0·59$	11495
21	East and SE. Mid-	36	13883	175	$1·26 \pm 0·67$	13001

TABLE XVIII.

ibution of Thyroid Enlargement at Age 12 in England and Wales, with proba

Areas (chiefly Rural).				Municipal Boroughs and Urban Districts.						
	Girls.				Boys.			Girls.		
of	Total examined.	Enlargement of Thyroid.		No. of M.O.'s taking part.	Total examined.	Enlargement of Thyroid.		Total examined.	Enlargement of Thyroid.	
		No.	%.			No.	%.		No.	%.
1·38	4817	1012	21·01 ± 2·02	7	721	8	1·11 ± 1·94	775	64	8·26 ± 2·5
0·97	2518	557	25·81 ± 1·59	4	841	27	3·21 ± 2·02	919	99	10·77 ± 3·3
1·71	3294	471	14·29 ± 2·80	3	454	1	0·22 ± 2·10	423	19	4·49 ± 3·6
0·86	5890	793	13·57 ± 1·34	17	4972	278	5·59 ± 1·06	5125	568	11·08 ± 1·6
0·55	16519	2833	17·15 ± 0·86	31	6988	314	4·49 ± 0·76	7242	750	10·36 ± 1·2
1·59	2765	563	20·36 ± 2·34	3	352	5	1·42 ± 2·19	356	24	6·74 ± 3·7
1·24	3597	606	16·84 ± 2·09	4	771	41	5·32 ± 2·17	760	114	15·00 ± 3·4
1·57	4047	648	16·01 ± 2·37	4	623	48	7·70 ± 2·34	559	81	14·50 ± 3·4
3·15	502	135	26·89 ± 4·72	—	—	—	—	—	—	—
3·46	999	213	21·32 ± 5·53	1	461	37	8·03 ± 4·72	514	99	19·26 ± 7·2
0·79	11910	2165	18·18 ± 1·22	12	2207	131	5·94 ± 1·28	2189	318	14·53 ± 2·0
0·45	28429	4998	17·58 ± 0·70	43	9195	445	4·84 ± 0·65	9431	1068	11·32 ± 1·0
0·89	8570	233	2·72 ± 1·49	22	7355	194	2·64 ± 0·85	7408	536	7·24 ± 1·3
0·85	6547	253	3·86 ± 1·44	14	5376	230	4·28 ± 1·12	5371	504	9·38 ± 1·7
0·67	13001	535	4·11 ± 1·13	28	6533	48	0·73 ± 0·70	6170	214	3·47 ± 1·2
0·56	16250	967	5·95 ± 0·92	27	6633	132	1·99 ± 0·75	6772	356	5·26 ± 1·2
1·24	4836	111	2·29 ± 2·10	18	4031	42	1·04 ± 0·88	4042	140	3·46 ± 1·4
0·34	49204	2099	4·26 ± 0·57	109	29928	646	2·16 ± 0·37	29763	1750	5·88 ± 0·62
0·70	15309	1181	7·71 ± 1·13	38	10776	399	3·70 ± 0·66	10798	938	8·68 ± 1·07
1·38	4817	1021	21·01 ± 2·02	7	721	8	1·11 ± 1·42	775	64	8·26 ± 2·50
0·94	8600	887	10·31 ± 1·49	22	4844	84	1·73 ± 0·82	4912	263	5·35 ± 1·37
·58	15281	1035	6·77 ± 0·95	21	5223	100	1·91 ± 0·84	5293	285	5·38 ± 1·41
·39	44007	4115	9·37 ± 0·62	88	21564	591	2·74 ± 0·43	21778	1550	7·12 ± 0·70
·71	9130	826	9·13 ± 1·21	17	6064	269	4·43 ± 1·02	6048	590	9·75 ± 1·62
·59	11495	1621	14·10 ± 0·94	19	4962	183	3·69 ± 0·94	5198	464	8·92 ± 1·52
·67	13001	535	4·11 ± 1·13	28	6533	48	0·73 ± 0·70	6170	214	3·47 ± 1·20

21	East and SE. Mid-	36	13883	175	1·26 ± 0·67	13001

TABLE XVIII.

and Wales, with probable errors due to Medical Officers' personal equations.

nd Urban Districts.			Administrative Counties (preceding groups combined).			County Boro			
Girls.						Boys.			
Total examined.	Enlargement of Thyroid.		Boys.	Girls.	No. of M.O.'s taking part.	Total examined.	Enlargement of Thyroid.		
	No.	%.	%.	%.			No.	%.	
775	64	$8·26 \pm 2·50$	$9·04 \pm 1·07$	$19·24 \pm 1·59$	4	1416	38	$2·68 \pm 1·99$	
919	99	$10·77 \pm 3·37$	$6·45 \pm 0·85$	$19·09 \pm 1·37$	1	359	4	$1·11 \pm 3·76$	
423	19	$4·49 \pm 3·68$	$4·33 \pm 1·37$	$13·18 \pm 2·25$	5	2198	37	$1·68 \pm 1·72$	
5125	568	$11·08 \pm 1·64$	$5·82 \pm 0·67$	$12·35 \pm 1·04$	5	3167	68	$2·14 \pm 1·74$	
7242	750	$10·36 \pm 1·20$	$6·41 \pm 0·44$	$15·08 \pm 0·69$	15	7140	147	$2·06 \pm 1·00$	
356	24	$6·74 \pm 3·75$	$8·89 \pm 1·33$	$18·81 \pm 1·99$	7	2619	11	$0·42 \pm 1·38$	
760	114	$15·00 \pm 3·49$	$4·43 \pm 1·06$	$16·52 \pm 1·78$	3	2170	5	$0·23 \pm 2·10$	
559	81	$14·50 \pm 3·47$	$7·72 \pm 1·29$	$15·83 \pm 1·94$	18	4991	189	$3·79 \pm 0·97$	
—	—	—	—	—	—	—	—	—	
514	99	$19·26 \pm 7·24$	$7·48 \pm 2·77$	$20·62 \pm 4·36$	1	192	15	$7·81 \pm 4·69$	
2189	318	$14·53 \pm 2·01$	$7·11 \pm 0·66$	$17·61 \pm 1·03$	29	9972	220	$2·21 \pm 0·72$	
9431	1068	$11·32 \pm 1·04$	$6·67 \pm 0·37$	$16·02 \pm 0·58$	44	17112	367	$2·14 \pm 0·59$	
7408	536	$7·24 \pm 1·39$	$1·68 \pm 0·61$	$4·81 \pm 1·02$	42	17144	227	$1·32 \pm 0·58$	
5371	504	$9·38 \pm 1·78$	$2·49 \pm 0·68$	$6·35 \pm 1·12$	28	10732	277	$2·58 \pm 0·75$	
6170	214	$3·47 \pm 1·20$	$1·09 \pm 0·48$	$3·91 \pm 0·82$	5	901	19	$2·11 \pm 1·74$	
6772	356	$5·26 \pm 1·24$	$2·23 \pm 0·45$	$5·61 \pm 0·73$	72	24236	95	$0·39 \pm 0·43$	
4042	140	$3·46 \pm 1·49$	$0·81 \pm 0·72$	$2·83 \pm 1·22$	3	732	5	$0·68 \pm 2·13$	
29763	1750	$5·88 \pm 0·62$	$1·71 \pm 0·25$	$4·87 \pm 0·42$	150	53745	623	$1·16 \pm 0·25$	
10798	938	$8·68 \pm 1·07$	$3·48 \pm 0·49$	$8·12 \pm 0·78$	64	24311	461	$1·89 \pm 0·48$	
775	64	$8·26 \pm 2·50$	$9·04 \pm 1·07$	$19·24 \pm 1·59$	4	1416	38	$2·68 \pm 1·99$	
4912	263	$5·35 \pm 1·37$	$3·51 \pm 0·63$	$8·51 \pm 1·01$	11	3543	31	$0·90 \pm 1·12$	
5293	285	$5·38 \pm 1·41$	$2·46 \pm 0·47$	$6·42 \pm 0·78$	46	16189	51	$0·31 \pm 0·54$	
21778	1550	$7·12 \pm 0·70$	$3·61 \pm 0·29$	$8·61 \pm 0·47$	125	45459	581	$1·28 \pm 0·34$	
6048	590	$9·75 \pm 1·62$	$3·09 \pm 0·57$	$9·33 \pm 0·96$	31	12902	282	$2·18 \pm 0·70$	
5198	464	$8·92 \pm 1·52$	$4·85 \pm 0·49$	$12·49 \pm 0·79$	33	11595	108	$0·93 \pm 0·65$	
6170	214	$3·47 \pm 1·20$	$1·09 \pm 0·48$	$3·91 \pm 0·82$	5	901	19	$2·11 \pm 1·74$	

0·67 | 13001 | 535 | 4·11 ± 1·13 | 28 | 6533 | 48 | 0·73 ± 0·70 | 6170 | 214 | 3·47 ± 1·20

...equations.

County Boroughs.				All Classes of Area combined.	
...ement of ...yroid.	Girls.				
	Total examined.	Enlargement of Thyroid.		Boys.	Girls.
%.		No.	%.	%.	%.
2·68 ± 1·99	1454	96	6·60 ± 3·25	7·69 ± 0·94	16·63 ± 1·44
1·11 ± 3·76	392	20	5·10 ± 6·41	5·94 ± 0·82	17·65 ± 1·33
1·68 ± 1·72	2106	122	5·79 ± 2·89	3·34 ± 1·07	10·51 ± 1·80
2·14 ± 1·74	3431	234	6·82 ± 2·92	4·99 ± 0·61	11·04 ± 0·97
2·06 ± 1·00	7383	472	6·39 ± 1·78	5·38 ± 0·40	13·02 ± 0·64
0·42 ± 1·38	2668	41	1·54 ± 2·35	5·07 ± 0·97	10·85 ± 1·52
0·23 ± 2·10	1983	28	1·41 ± 3·57	2·98 ± 0·93	11·79 ± 1·57
3·79 ± 0·97	4976	701	14·08 ± 1·63	5·66 ± 0·80	14·92 ± 1·27
—	—	—	—	—	—
7·81 ± 4·69	182	32	17·58 ± 7·14	7·52 ± 2·40	20·29 ± 3·77
2·21 ± 0·72	9809	802	8·17 ± 1·26	5·07 ± 0·50	13·74 ± 0·80
2·14 ± 0·59	17192	1274	7·41 ± 0·99	5·26 ± 0·35	13·33 ± 0·56
1·32 ± 0·58	16196	749	4·62 ± 0·98	1·50 ± 0·43	4·72 ± 0·72
2·58 ± 0·75	10316	694	6·73 ± 1·23	2·53 ± 0·51	6·53 ± 0·84
2·11 ± 1·74	1170	68	5·81 ± 2·89	1·13 ± 0·47	4·02 ± 0·79
0·39 ± 0·43	23830	410	1·72 ± 0·73	1·29 ± 0·31	3·68 ± 0·52
0·68 ± 2·13	743	20	2·70 ± 3·62	0·80 ± 0·69	2·82 ± 1·17
1·16 ± 0·25	52255	1941	3·71 ± 0·42	1·49 ± 0·20	4·41 ± 0·33
1·89 ± 0·48	27925	1618	5·79 ± 0·80	2·71 ± 0·35	6·92 ± 0·57
2·68 ± 1·99	1454	96	6·60 ± 3·25	7·69 ± 0·94	16·63 ± 1·44
0·90 ± 1·12	3593	93	2·58 ± 1·89	2·96 ± 0·55	7·27 ± 0·90
0·31 ± 0·54	15376	215	1·40 ± 0·92	1·52 ± 0·36	4·27 ± 0·60
1·28 ± 0·34	44186	2022	4·58 ± 0·57	2·65 ± 0·22	6·99 ± 0·36
2·18 ± 0·70	12299	722	5·87 ± 1·16	2·68 ± 0·45	7·78 ± 0·75
0·93 ± 0·65	11892	403	3·39 ± 1·10	3·23 ± 0·39	8·70 ± 0·64
2·11 ± 1·74	1170	68	5·81 ± 2·89	1·13 ± 0·47	4·02 ± 0·79

Girls. | Boys. | Girls.

6170	214	3·47 ± 1·20	1·09 ± 0·48	3·91 ± 0·82	5	901	19	2·11 ± 1·74

Key No. of Area	Definition of Areas based upon (a) Goitre prevalence, (b) Geographical position.	No. of M.O.'s taking part.	Boys. Total examined.	Boys. Enlargement of Thyroid. No.	Boys. Enlargement of Thyroid. %.	Total examined.	N
	(a) *Areas of high prevalence*—						
1	South-western Counties	15	4568	470	10·29 ± 1·38	4817	10
2	South Midland area	26	2506	189	7·54 ± 0·97	2518	5
3	East Central area	7	3239	159	4·91 ± 1·71	3294	4
4	South Pennine area	30	5974	359	6·01 ± 0·86	5890	7
1–4	Total 'goitre belt'	78	16287	1177	7·23 ± 0·55	16519	28
5	Hampshire and Isle of Wight	11	2830	278	9·83 ± 1·59	2765	5
6	Worcester to Carmarthen	13	3355	142	4·23 ± 1·24	3597	6
7	Cheshire to Carnarvon	10	3899	301	7·72 ± 1·57	4047	6
8	W. Northumberland and Weardale	3	520	57	10·96 ± 3·15	502	1
9	SW. Kent and part of Sussex	2	1036	75	7·24 ± 3·46	999	2
5–9	Total subsidiary areas	39	11640	853	7·33 ± 0·79	11910	21
1–9	Total areas of high prevalence	117	27927	2030	7·28 ± 0·45	28429	49
	Areas of low prevalence—						
10	Western Seaboard area	20	8978	80	0·89 ± 0·89	8570	2
11	W. Midlands and Central Wales	22	6779	73	1·08 ± 0·85	6547	2
12	East and SE. Midlands	36	13883	175	1·26 ± 0·67	13001	5
13	East Seaboard and West Riding	55	16689	387	2·33 ± 0·56	16250	9
14	Southern Seaboard area	10	4512	27	0·60 ± 1·24	4836	1
10–14	Total areas of low prevalence	143	50841	742	1·46 ± 0·34	49204	20
	(b) *Geographical Divisions*—						
15	West Seaboard Counties	38	15263	506	3·31 ± 0·70	15309	11
16	South-western Counties	15	4568	470	10·29 ± 1·38	4817	10
17	South Seaboard Counties	23	8378	380	4·53 ± 0·94	8600	8
18	Eastern Seaboard Counties	53	15699	414	2·64 ± 0·58	15281	10
	Total Seaboard Counties	129	43908	1770	4·03 ± 0·39	44007	41
19	W. Midland and Border Counties	34	9435	210	2·23 ± 0·71	9130	8
20	E. Central and S. Midland Counties	61	11542	617	5·34 ± 0·59	11495	16
21	East and SE. Midland Counties	36	13883	175	1·26 ± 0·67	13001	5
	Total Inland Counties	131	34860	1002	2·58 ± 0·37	33626	29
	Total England and Wales	260	78768	2772	3·52 ± 0·27	77633	70
	Total Coast Towns	—	—	—	—	—	—
	Total Inland Towns	—	—	—	—	—	—

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
·11 ± 1·74	1170	68	5·81 ± 2·89	1·13 ± 0·47	4·02 ± 0·79

Girls.				Boys.			Girls.		
Total examined.	Enlargement of Thyroid. No.	Enlargement of Thyroid. %.	No. of M.O.'s taking part.	Total examined.	Enlargement of Thyroid. No.	Enlargement of Thyroid. %.	Total examined.	Enlargement of Thyroid. No.	Enlargement of Thyroid. %.
4817	1012	21·01 ± 2·02	7	721	8	1·11 ± 1·94	775	64	8·26 ± 2·50
2518	557	25·81 ± 1·59	4	841	27	3·21 ± 2·02	919	99	10·77 ± 3·37
3294	471	14·29 ± 2·80	3	454	1	0·22 ± 2·10	423	19	4·49 ± 3·68
5890	793	13·57 ± 1·34	17	4972	278	5·59 ± 1·06	5125	568	11·08 ± 1·64
16519	2833	17·15 ± 0·86	31	6988	314	4·49 ± 0·76	7242	750	10·36 ± 1·20
2765	563	20·36 ± 2·34	3	352	5	1·42 ± 2·19	356	24	6·74 ± 3·75
3597	606	16·84 ± 2·09	4	771	41	5·32 ± 2·17	760	114	15·00 ± 3·49
4047	648	16·01 ± 2·37	4	623	48	7·70 ± 2·34	559	81	14·50 ± 3·47
502	135	26·89 ± 4·72	—	—	—	—	—	—	—
999	213	21·32 ± 5·53	1	461	37	8·03 ± 4·72	514	99	19·26 ± 7·24
11910	2165	18·18 ± 1·22	12	2207	131	5·94 ± 1·28	2189	318	14·53 ± 2·01
28429	4998	17·58 ± 0·70	43	9195	445	4·84 ± 0·65	9431	1068	11·32 ± 1·04
8570	233	2·72 ± 1·49	22	7355	194	2·64 ± 0·85	7408	536	7·24 ± 1·39
6547	253	3·86 ± 1·44	14	5376	230	4·28 ± 1·12	5371	504	9·38 ± 1·78
13001	535	4·11 ± 1·13	28	6533	48	0·73 ± 0·70	6170	214	3·47 ± 1·20
16250	967	5·95 ± 0·92	27	6633	132	1·99 ± 0·75	6772	356	5·26 ± 1·24
4836	111	2·29 ± 2·10	18	4031	42	1·04 ± 0·88	4042	140	3·46 ± 1·49
49204	2099	4·26 ± 0·57	109	29928	646	2·16 ± 0·37	29763	1750	5·88 ± 0·62
15309	1181	7·71 ± 1·13	38	10776	399	3·70 ± 0·66	10798	938	8·68 ± 1·07
4817	1021	21·01 ± 2·02	7	721	8	1·11 ± 1·42	775	64	8·26 ± 2·50
8600	887	10·31 ± 1·49	22	4844	84	1·73 ± 0·82	4912	263	5·35 ± 1·37
15281	1035	6·77 ± 0·95	21	5223	100	1·91 ± 0·84	5293	285	5·38 ± 1·41
44007	4115	9·37 ± 0·62	88	21564	591	2·74 ± 0·43	21778	1550	7·12 ± 0·70
9130	826	9·13 ± 1·21	17	6064	269	4·43 ± 1·02	6048	590	9·75 ± 1·62
11495	1621	14·10 ± 0·94	19	4962	183	3·69 ± 0·94	5198	464	8·92 ± 1·52
13001	535	4·11 ± 1·13	28	6533	48	0·73 ± 0·70	6170	214	3·47 ± 1·20
33626	2982	8·75 ± 0·62	64	17559	500	2·85 ± 0·50	17416	1268	7·28 ± 0·82
77633	7097	9·14 ± 0·43	152	39123	1091	2·79 ± 0·32	39194	2818	7·19 ± 0·53
—	—	—	24	4844	93	1·92 ± 0·79	4789	220	4·59 ± 1·31
—	—	—	128	34279	998	2·91 ± 0·36	34405	2598	7·55 ± 0·58

f	Girls.			(preceding groups combined).		No. of M.O.'s taking part.	Boys.		
	Total examined.	Enlargement of Thyroid.		Boys.	Girls.		Total examined.	Enlargement of Thyroid.	
		No.	%.	%.	%.			No.	%.
94	775	64	8·26 ± 2·50	9·04 ± 1·07	19·24 ± 1·59	4	1416	38	2·68 ± 1·99
02	919	99	10·77 ± 3·37	6·45 ± 0·85	19·09 ± 1·37	1	359	4	1·11 ± 3·76
10	423	19	4·49 ± 3·68	4·33 ± 1·37	13·18 ± 2·25	5	2198	37	1·68 ± 1·72
06	5125	568	11·08 ± 1·64	5·82 ± 0·67	12·35 ± 1·04	5	3167	68	2·14 ± 1·74
76	7242	750	10·36 ± 1·20	6·41 ± 0·44	15·08 ± 0·69	15	7140	147	2·06 ± 1·00
19	356	24	6·74 ± 3·75	8·89 ± 1.33	18·81 ± 1·99	7	2619	11	0·42 ± 1·38
17	760	114	15·00 ± 3·49	4·43 ± 1·06	16·52 ± 1·78	3	2170	5	0·23 ± 2·10
34	559	81	14·50 ± 3·47	7·72 ± 1·29	15·83 ± 1·94	18	4991	189	3·79 ± 0·97
	—	—	—	—	—	—	—	—	—
72	514	99	19·26 ± 7·24	7·48 ± 2·77	20·62 ± 4·36	1	192	15	7·81 ± 4·69
28	2189	318	14·53 ± 2·01	7·11 ± 0·66	17·61 ± 1·03	29	9972	220	2·21 ± 0·72
65	9431	1068	11·32 ± 1·04	6·67 ± 0·37	16·02 ± 0·58	44	17112	367	2·14 ± 0·59
85	7408	536	7·24 ± 1·39	1·68 ± 0·61	4·81 ± 1·02	42	17144	227	1·32 ± 0·58
12	5371	504	9·38 ± 1·78	2·49 ± 0·68	6·35 ± 1·12	28	10732	277	2·58 ± 0·75
70	6170	214	3·47 ± 1·20	1·09 ± 0·48	3·91 ± 0·82	5	901	19	2·11 ± 1·74
75	6772	356	5·26 ± 1·24	2·23 ± 0·45	5·61 ± 0·73	72	24236	95	0·39 ± 0·43
38	4042	140	3·46 ± 1·49	0·81 ± 0·72	2·83 ± 1·22	3	732	5	0·68 ± 2·13
37	29763	1750	5·88 ± 0·62	1·71 ± 0·25	4·87 ± 0·42	150	53745	623	1·16 ± 0·25
66	10798	938	8·68 ± 1·07	3·48 ± 0·49	8·12 ± 0·78	64	24311	461	1·89 ± 0·48
2	775	64	8·26 ± 2·50	9·04 ± 1·07	19·24 ± 1·59	4	1416	38	2·68 ± 1·99
2	4912	263	5·35 ± 1·37	3·51 ± 0·63	8·51 ± 1·01	11	3543	31	0·90 ± 1·12
4	5293	285	5·38 ± 1·41	2·46 ± 0·47	6·42 ± 0·78	46	16189	51	0·31 ± 0·54
3	21778	1550	7·12 ± 0·70	3·61 ± 0·29	8·61 ± 0·47	125	45459	581	1·28 ± 0·34
2	6048	590	9·75 ± 1·62	3·09 ± 0·57	9·33 ± 0·96	31	12902	282	2·18 ± 0·70
4	5198	464	8·92 ± 1·52	4·85 ± 0·49	12·49 ± 0·79	33	11595	108	0·93 ± 0·65
0	6170	214	3·47 ± 1·20	1·09 ± 0·48	3·91 ± 0·82	5	901	19	2·11 ± 1·74
0	17416	1268	7·28 ± 0·82	2·87 ± 0·29	8·33 ± 0·49	69	25398	409	1·61 ± 0·46
2	39194	2818	7·19 ± 0·53	3·27 ± 0·20	8·49 ± 0·34	194	70857	990	1·40 ± 0·27
9	4789	220	4·59 ± 1·31	—	—	62	22814	173	0·76 ± 0·47
6	34405	2598	7·55 ± 0·58	—	—	132	48043	817	1·70 ± 0·33

…ement of …yroid.	Girls.			combined.	
	Total examined.	Enlargement of Thyroid.		Boys.	Girls.
%.		No.	%.	%.	%.
2·68 ± 1·99	1454	96	6·60 ± 3·25	7·69 ± 0·94	16·63 ± 1·44
1·11 ± 3·76	392	20	5·10 ± 6·41	5·94 ± 0·82	17·65 ± 1·33
1·68 ± 1·72	2106	122	5·79 ± 2·89	3·34 ± 1·07	10·51 ± 1·80
2·14 ± 1·74	3431	234	6·82 ± 2·92	4·99 ± 0·61	11·04 ± 0·97
2·06 ± 1·00	7383	472	6·39 ± 1·78	5·38 ± 0·40	13·02 ± 0·64
0·42 ± 1·38	2668	41	1·54 ± 2·35	5·07 ± 0·97	10·85 ± 1·52
0·23 ± 2·10	1983	28	1·41 ± 3·57	2·98 ± 0·93	11·79 ± 1·57
3·79 ± 0·97	4976	701	14·08 ± 1·63	5·66 ± 0·80	14·92 ± 1·27
—	—	—	—	—	—
7·81 ± 4·69	182	32	17·58 ± 7·14	7·52 ± 2·40	20·29 ± 3·77
2·21 ± 0·72	9809	802	8·17 ± 1·26	5·07 ± 0·50	13·74 ± 0·80
2·14 ± 0·59	17192	1274	7·41 ± 0·99	5·26 ± 0·35	13·33 ± 0·56
1·32 ± 0·58	16196	749	4·62 ± 0·98	1·50 ± 0·43	4·72 ± 0·72
2·58 ± 0·75	10316	694	6·73 ± 1·23	2·53 ± 0·51	6·53 ± 0·84
2·11 ± 1·74	1170	68	5·81 ± 2·89	1·13 ± 0·47	4·02 ± 0·79
0·39 ± 0·43	23830	410	1·72 ± 0·73	1·29 ± 0·31	3·68 ± 0·52
0·68 ± 2·13	743	20	2·70 ± 3·62	0·80 ± 0·69	2·82 ± 1·17
1·16 ± 0·25	52255	1941	3·71 ± 0·42	1·49 ± 0·20	4·41 ± 0·33
1·89 ± 0·48	27925	1618	5·79 ± 0·80	2·71 ± 0·35	6·92 ± 0·57
2·68 ± 1·99	1454	96	6·60 ± 3·25	7·69 ± 0·94	16·63 ± 1·44
0·90 ± 1·12	3593	93	2·58 ± 1·89	2·96 ± 0·55	7·27 ± 0·90
0·31 ± 0·54	15376	215	1·40 ± 0·92	1·52 ± 0·36	4·27 ± 0·60
1·28 ± 0·34	44186	2022	4·58 ± 0·57	2·65 ± 0·22	6·99 ± 0·36
2·18 ± 0·70	12299	722	5·87 ± 1·16	2·68 ± 0·45	7·78 ± 0·75
0·93 ± 0·65	11892	403	3·39 ± 1·10	3·23 ± 0·39	8·70 ± 0·64
2·11 ± 1·74	1170	68	5·81 ± 2·89	1·13 ± 0·47	4·02 ± 0·79
1·61 ± 0·46	25361	1173	4·70 ± 0·77	2·46 ± 0·25	7·12 ± 0·42
1·40 ± 0·27	69447	3215	4·63 ± 0·46	2·57 ± 0·17	7·05 ± 0·27
0·76 ± 0·47	22586	667	2·95 ± 0·80	—	—
1·70 ± 0·33	46861	2548	5·44 ± 0·56	—	—

In Table XVI the same information is given for urban districts and municipal boroughs having independent education authorities, these being tabulated under the counties in which they are located. The numbers of the divisions to which they have been allocated are again given, since in defining the goitre areas an attempt has been made in some cases to define the boundaries of these divisions more precisely than by the county boundaries.

In Table XVII the returns from the county boroughs are given, these being arranged as before under the respective counties in which they are situated.

In the lower part of Table XVIII the country has been divided up into seven geographical divisions (Nos. 15–21) without reference to goitre prevalence, separating four groups of counties bordering the sea-coast and three groups of counties entirely inland. The definition of these groups is as follows:

No. 15. West Seaboard. Cumberland, Lancashire, Cheshire, Flint, Denbighshire, Carnarvonshire, Merionethshire, Cardiganshire, Pembrokeshire, Carmarthenshire, Glamorganshire.

No. 16. S.-W. Counties. Somersetshire, Devonshire, Cornwall.

No. 17. South Seaboard. Kent, Sussex, Hampshire, Isle of Wight, Dorsetshire.

No. 18. East Seaboard. Northumberland, Durham, Yorkshire North and East Ridings and City of York, Lincolnshire, Norfolk, Suffolk, Essex.

No. 19. W. Midland and Border Counties. Montgomeryshire, Radnorshire, Brecknockshire, Monmouthshire, Gloucestershire, Shropshire, Herefordshire, Staffordshire, Warwickshire, Worcestershire.

No. 20. E. Central and S. Midland Counties. Derbyshire, Yorkshire West Riding, Nottinghamshire, Leicestershire, Rutland, Soke and Borough of Peterborough, Northamptonshire, Oxfordshire, Buckinghamshire, Wiltshire.

No. 21. E. and S.-E. Midland Counties. Huntingdonshire, Cambridgeshire and Isle of Ely, Bedfordshire, Hertfordshire, Middlesex (excluding London), Berkshire, Surrey.

Examination of the mean rates for the county areas in these groups shows the South-Western group to stand out with a high rate of 15·65 per cent. Next comes the East Central and South Midland group with 9·64 per cent., followed by the South Seaboard counties with 7·42 per cent. The lowest rates are given by the East Seaboard counties with 4·70 per cent. and the East and South-East Midland group with 2·69 per cent. We may here notice the effect of *proximity to the sea*, which is brought out as follows:

TABLE XIX.

	County Areas.		Urban Districts and Boroughs.		County Boroughs.	
	Boys.	Girls.	Boys.	Girls.	Boys.	Girls.
Counties bordering the sea-coast:						
Divisions 15–18	4·03 ± 0·39	9·37 ± 0·62	2·74 ± 0·43	7·12 ± 0·70	1·28 ± 0·34	4·58 ± 0·57
Divisions 15, 17, 18 only	3·30 ± 0·41	7·92 ± 0·65	2·80 ± 0·45	7·07 ± 0·73	1·25 ± 0·34	4·40 ± 0·58
Inland counties:						
Divisions 19–21	2·58 ± 0·37	8·75 ± 0·62	2·85 ± 0·50	7·28 ± 0·82	1·61 ± 0·46	4·70 ± 0·77
Coast towns	—	—	1·92 ± 0·79	4·59 ± 1·31	0·76 ± 0·47	2·95 ± 0·80
Inland towns	—	—	2·91 ± 0·36	7·55 ± 0·58	1·70 ± 0·33	5·44 ± 0·56

The South-West counties with their very high goitre frequency raise the average for the Seaboard counties considerably; if these be excluded and the remaining groups 15, 17, 18 taken together, the aggregate rates are not significantly different from the corresponding rates for inland counties. Considered in this way by taking a broad band all round the coast, no effect of proximity to the sea is evident. I have therefore separated the small and large towns into two groups, those actually on the coast and those inland; the group to which each town has been allocated is indicated in Tables XVI–XVII by the letters 'S' and 'I'. When this is done the coast towns have lower average rates than inland towns; for girls the difference is undoubtedly significant for county boroughs and exceeds twice its probable error for small towns; for boys the differences are about one and a half times their probable errors.

The effect of proximity to the sea is therefore probably a definite one, but we must conclude that it is confined to the immediate coast line. The Devon coast is an exception; other towns with rates which are possibly significantly high and which lie close to the sea are Blackpool, Hastings, Wallasey, and Preston.

Returning to the seven geographical divisions, the lowest rates are given by the East and South-East Midland group, viz. $1{\cdot}26 \pm 0{\cdot}67$ for boys and $4{\cdot}11 \pm 1{\cdot}13$ for girls in the rural areas alone, or $1{\cdot}13 \pm 0{\cdot}47$ and $4{\cdot}02 \pm 0{\cdot}79$ in rural districts and towns combined. This suggests the values 1 per cent. in boys and 4 per cent. in girls as the 'normal' basal values from which to measure. After excluding the 'goitre areas' by the method to be explained, the remainder, or total 'non-goitrous' area of the country, gives rates $1{\cdot}45 \pm 0{\cdot}34$ and $4{\cdot}26 \pm 0{\cdot}57$ for the rural districts and $1{\cdot}49 \pm 0{\cdot}20$ and $4{\cdot}41 \pm 0{\cdot}33$ for rural areas and towns combined in boys and girls respectively; these residual rates lend support to the use of 1 and 4 per cent. as measures of normality.

The method used in defining the geographical distribution of thyroid enlargement was therefore to search for districts or combinations of districts whose aggregate thyroid rates were, on the basis of their probable errors derived by the formulae of Table IX, significantly higher than 1 or 4 per cent. respectively in boys and girls. The criterion for significance was that the rate should differ from 1 or 4 per cent. by at least three times the probable error.

A few individual counties satisfy this criterion when taken by themselves: these are Cornwall, Devonshire, Somersetshire, Wiltshire, Hampshire, Isle of Wight, Worcestershire, Oxfordshire, Derbyshire, Lancashire, and perhaps the County of Durham. Here we have at once a rough indication of a distribution extending from the South-West to the Midlands and again appearing in the Pennine region. By next examining the rates in counties or parts of counties contingent on these, and proceeding to add such contiguous districts as showed rates well above the normal so long as the aggregate rate for the total continuous area remained significantly high as defined above, the boundaries of what I have called the 'goitre areas' have been approximately defined. It is obvious that owing to the large effect of the personal equation on the rates, these boundaries can only

be approximate, but the method outlined defines what are the most probable boundaries. In any case these areas are not usually marked by any sharp line, since the prevalence of thyroid enlargement tends to increase slowly as we approach the endemic areas.

As an example of the method used, take the case of the North Wales offshoot from the Pennine region of the 'main goitre belt'. Starting westwards from North Derbyshire and South Lancashire, it is found that three of the four districts of Cheshire, when combined, give rates which are significantly above 1 and 4 per cent. in boys and girls; adjacent to this is Denbighshire with 10·41 per cent. in boys and 14·51 per cent. in girls, as found by two medical officers, figures which would be significantly high in themselves if the probable error formula could be safely applied for $n = 2$; adjacent to Denbighshire is Carnarvonshire with 3·48 per cent. in boys and 10·95 per cent. in girls, also due to two medical officers, and continuous with this is Merionethshire with 5·26 per cent. and 14·23 per cent., all these being high rates as they stand. Exploring in all directions from this region, except at the Pennine end, low rates are found, and it therefore seems reasonable to consider this continuous area together, leading to a result, now based on ten medical officers, of $7{\cdot}72 \pm 1{\cdot}57$ per cent. in boys and $16{\cdot}01 \pm 2{\cdot}37$ per cent. in girls, both figures being almost five times their probable errors above the normal basis. That there is such an offshoot in which prevalence is high can therefore be regarded as certain, but it can only be stated that the boundaries indicated are approximate boundaries.

Proceeding in this way and also searching elsewhere for isolated centres of high prevalence, the 'goitre areas' shown in Table XVIII have been defined. The South-West endemic centre is found to join up in a continuous band through parts of Gloucestershire, Oxfordshire, Buckinghamshire, Leicestershire, Northamptonshire, Rutland, and Nottinghamshire to Derbyshire. There is thus a continuous belt of high incidence extending from Cornwall through Somersetshire, between the Cotswold and Chiltern Hills into Northamptonshire, then bending north and eventually north-west across the southern portion of Nottinghamshire into Derbyshire, whence it extends up the Pennine chain. How far it extends northwards is unfortunately not possible to say, since rural data from Westmorland and Cumberland are lacking.

From this curved belt, concave to the west, there appear to be three or more offshoots, the first extending south-east through Hampshire to the Isle of Wight, the second extending west from North Gloucestershire through Herefordshire to Carmarthenshire, the third extending across Cheshire to North Wales.

Another region with significantly high rates is found in West Northumberland and Durham; it will probably be found that this is continuous with the Pennine belt through Westmorland and Cumberland. Another centre is to be found in South-West Kent and part of Sussex, which may be the end of an eastward extension from Hampshire between the North and South Downs, though this remains doubtful.

For convenience the main belt has been subdivided into four areas, and the definitions of the Divisions 1 to 9 in Table XVIII are as follows:

No. 1. *South-West Counties.* Somersetshire; Devonshire; Cornwall.

No. 2. *South Midland area.* Oxfordshire; Buckinghamshire; Wiltshire;

Eastern half of Gloucestershire (districts of Campden, Chipping Sodbury, Cirencester, Faringdon, Marston Sicca, Nailsworth, Northleach, Petworth, Stow-on-the-Wold, Stroud, Tetbury, Winchcombe).

No. 3. *East Central area.* Leicestershire; Rutland; Northamptonshire; Soke and Borough of Peterborough.

No. 4. *South Pennine area.* Derbyshire; Nottinghamshire, excluding north-east county area, but including Mansfield; Yorkshire, West Riding county areas of Skipton and Ilkley and Boroughs of Keighley and Todmorden; Cheshire, Boroughs of Hyde and Stalybridge; Lancashire, county areas of South Ribble, North Chorley, Rishton, Blackburn Rural District, Barrowford, Brierfield, Padiham, Turton, Ramsbottom and Tottington, Urban District of Chadderton, Boroughs of Accrington, Ashton-under-Lyne, Bacup, Chorley, Colne, Darwen, Mossley and Rawtenstall, County Boroughs of Blackburn, Burnley, and Rochdale.

No. 5. *Hampshire and Isle of Wight.*

No. 6. *Worcestershire to Carmarthenshire.* Worcestershire, Herefordshire, Brecknockshire, Carmarthenshire.

No. 7. *Cheshire to Carnarvonshire.* Lancashire, county areas of Kearsley, Prestwich, and Newton-in-Makerfield, County Borough of Manchester; Cheshire, North-east, west, and south-west county areas, Boroughs of Crewe and Congleton, County Boroughs of Stockport, Chester, and Wallasey; Denbighshire; Merionethshire; Carnarvonshire.

No. 8. *West Northumberland and Weardale.* Northumberland western county area (Bellingham, Glendale, Haltwhistle, Hexham, Prudhoe, Rothbury); Durham county area of Upper Weardale.

No. 9. *South-West Kent and part of Sussex.* Kent, county area of Cranbrook and Borough of Tunbridge Wells; Sussex East, western county area and County Borough of Hastings.

The residue of England and Wales has been divided into five areas for convenience, roughly coincident with the remnants of the geographical divisions 15, 17, 18, 19, 20, and 21; their exact definitions are as follows:

No. 10. *West Seaboard area.* Cumberland; Lancashire, excluding areas enumerated in Nos. 4, 7 above; Cheshire County Borough of Birkenhead; Flintshire; Anglesey; Cardiganshire; Pembrokeshire; Glamorganshire.

No. 11. *West Midlands and Central Wales.* Montgomeryshire; Radnorshire; Monmouthshire; Shropshire; Staffordshire; Warwickshire; Gloucestershire, western half (i.e. excluding the districts enumerated in No. 2 above), including Borough of Cheltenham and County Boroughs of Bristol and Gloucester; Cheshire 'Mid' county area.

No. 12. *East and South-East Midlands.* Same as No. 21.

No. 13. *East Seaboard and West Riding.* Northumberland, excluding the western districts enumerated in No. 8 above; Durham, excluding Upper Weardale; Yorkshire, North and East Ridings and City of York: Yorkshire, West Riding, excluding the areas mentioned in No. 4 above; Nottinghamshire north-east county area; Lincolnshire: Lindsey, Kesteven, and Holland; Norfolk; Suffolk; Essex.

No. 14. *Southern Seaboard area.* Kent, excluding Cranbrook county area and Tunbridge Wells; Sussex, excluding areas mentioned in No. 9 above; Dorsetshire.

For the purpose of constructing Fig. 4, a gradation of intensity has been attempted, and the following grouping has been regarded as most satisfactory, in the presence of the probable errors we have to deal with:

Intensity Scale.		Rate of Thyroid Enlargement in Boys aged 12.	Rate of Thyroid Enlargement in Girls aged 12.
0	Non-goitrous	Not significantly over 1 % in rural districts or small towns	Not significantly over 4 % in whole population including large towns
I	Transitional		Significantly over 4 % in whole population
II	Transitional		Significantly over 5 % in whole population and over 6 % in rural districts + small towns
III	Goitrous	Significantly over 1 % in rural districts + small towns	Significantly over 6 % in whole population and over 9 % in rural districts + small towns
IV	Goitrous	Significantly over 3 % in rural districts + small towns	Significantly over 8 % in whole population and over 9 % in rural districts + small towns
V	Goitrous	Significantly over 4 % in rural districts + small towns	Significantly over 12 % in whole population and over 14 % in rural districts + small towns

Under this classification the divisions are grouped as follows: Class 0, Nos. 10, 12, 13, 14; Class I, No. 11; Class II, Nos. 3, 9; Class III, Nos. 5, 6; Class IV, Nos. 4, 7; Class V, Nos. 1, 2. The shading on Fig. 4 has been carried out on this basis. It is evident that the most intense prevalence is along the main belt from Cornwall as far as Buckinghamshire; the Midland portion has only mild prevalence, which becomes more intense again on reaching Derbyshire and Lancashire.

The areas will now be dealt with individually, noting any points of special interest which arise from the school medical officers' returns.

South-West Counties (No. 1). The rates for the three counties are all high in the rural areas, viz.:

Cornwall,	Boys	4.84 ± 2.27 per cent.	Girls	17.05 ± 3.78 per cent.
Devon	„	8.38 ± 2.07 „	„	18.57 ± 3.13 „
Somerset	„	19.52 ± 3.00 „	„	28.70 ± 3.78 „

In the towns the mean rates for girls are also above normal. From my own observations in *Devon* and *Somerset*, summarized in Table XX, and the direct estimation of the personal equations of the medical officers who took part, it is possible to form more detailed conclusions here than elsewhere. Briefly these conclusions indicate a region of very high prevalence extending from Exmoor to the south coast of Devon east of the Exe. Other regions on the high ground of East Somerset and to the north-west of Dartmoor, particularly Okehampton, have also a high incidence, as have certain localities to the east and south of Dartmoor, notably Crediton, Ashburton, Bovey Tracey, and Tiverton. It is interesting to note that Weston-super-Mare has a very low rate as compared with most of Somerset, a fact which may be connected with its extensive sands, reputed to be rich in iodine.

South-Midland area with Hampshire and Isle of Wight (Nos. 2, 5). Passing north-east from Somerset, prevalence remains high in *Wiltshire*, with a mean rate for boys and girls of 17·8 per cent., with probable error about 3 per cent.

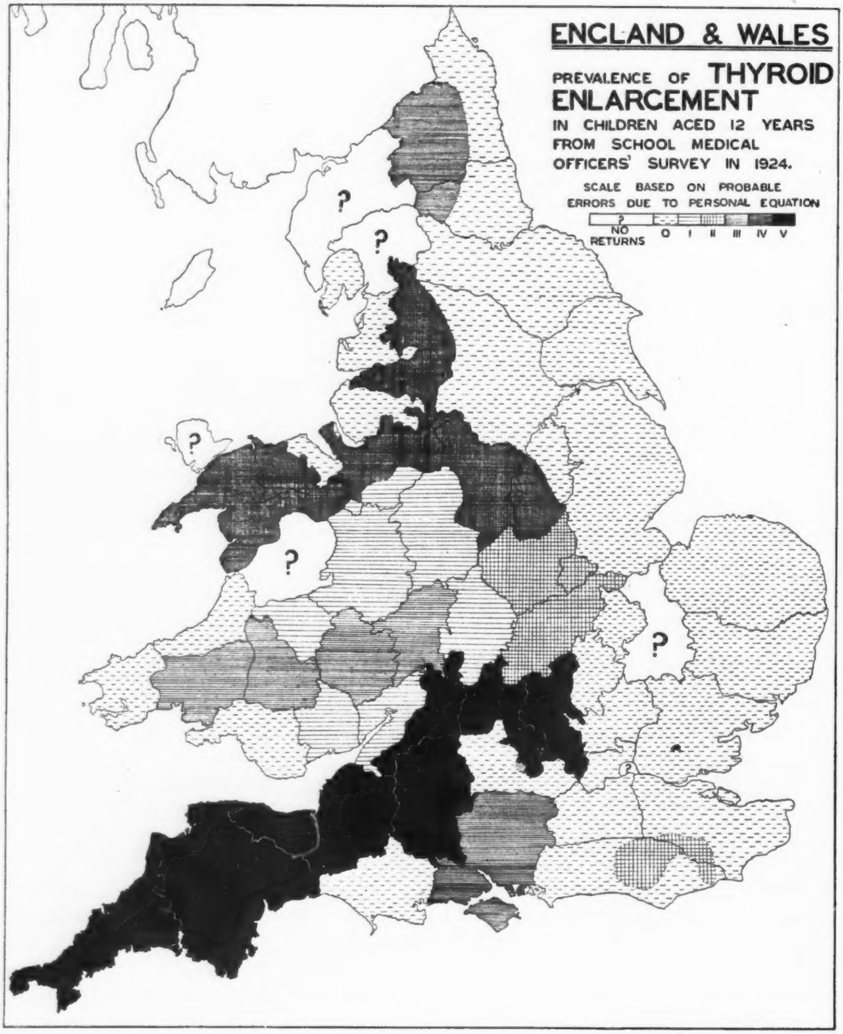
ENGLAND & WALES
PREVALENCE OF THYROID ENLARGEMENT
IN CHILDREN AGED 12 YEARS
FROM SCHOOL MEDICAL
OFFICERS' SURVEY IN 1924.
SCALE BASED ON PROBABLE
ERRORS DUE TO PERSONAL EQUATION
?
NO RETURNS
O I II III IV V
?
?
?
?
?

FIG. 4.

Gloucestershire is naturally divided into an easterly upland portion and a westerly portion consisting of the Severn Valley. The Medical Officer of Health, Dr. J. M. Martin, demonstrated that, according to the combined figures for 1911–20, goitre is much more prevalent in the Cotswold districts than in other parts of the county. If we divide the county by a line passing along the western boundaries of the districts of Chipping Sodbury, Tetbury, Nailsworth, Stroud, Cirencester, Northleach, Winchcombe, and Petworth, the resulting totals from 1911–20 inspection figures are:

	Boys.			Girls.		
	Examined.	+	Rate.	Examined.	+	Rate.
Western portion	8,876	64	0·721	9,122	321	3·519
Eastern portion	6,885	136	1·975	7,191	607	8·441

In 1924, using the new standard, 1,885 boys and 1,887 girls were examined, of whom 40 and 150 respectively showed enlargement; in the absence of precise details these totals have been divided in the same ratios as the 1911–20 figures and the estimates entered in Table XV; thus the rate for girls becomes 11·8 per cent. in the eastern area, which seems to justify its inclusion in the goitre area. Dorsetshire and Berkshire have low rates recorded, but *Hampshire* has a rate for girls of $13{\cdot}28 \pm 2{\cdot}44$, which is significantly above 4 per cent., and the *Isle of Wight* has the unusually high rate of 36 per cent. recorded for girls. There is little doubt, therefore, that a region of high prevalence extends from Wiltshire to the Isle of Wight. The Medical Officer of Health for *Dorset*, Dr. J. E. Robinson, remarks upon a decline in goitre prevalence since 1909, the rates in 'leavers' being for girls 16·9 per cent. in 1909, 11·5 per cent. in 1910, and 1·1 per cent. in 1924; whether this extraordinary change can be explained by change of observers during the period is difficult to say, but the present position of Dorsetshire on the goitre map seems somewhat anomalous.

Continuing in a north-east direction, *Oxfordshire* has very high rates based on seventeen medical officers, viz. $11{\cdot}39 \pm 1{\cdot}34$ per cent. in boys and $37{\cdot}22 \pm 2{\cdot}14$ per cent. in girls. *Buckinghamshire* gives 7·58 per cent. in boys and 11·46 per cent. in girls, which are high, though not significantly so by themselves.

Worcestershire and South Wales (No. 6). *Worcestershire* gives a mean rate of 9·16 per cent., based on nine medical officers, which appears to be significantly above the normal $2\frac{1}{2}$ per cent. The adjacent *Warwickshire* and *Shropshire* have low rates recorded, but the figures for subdivisions of the latter county suggest a somewhat higher rate in the south than elsewhere. Passing west, *Herefordshire*, with the town of Hereford, gives high rates, and it seems probable, though not certain, that this region of high incidence extends through *Brecknockshire* into *Carmarthenshire*. The surrounding counties of Monmouth, Glamorgan, Pembroke, Cardigan, and Radnor have only average rates returned.

East-Central area (No. 3). Passing east from Buckinghamshire we find average or low rates recorded as far as the east coast, but to the north there seems to be a band of somewhat high prevalence joining Oxfordshire and Buckinghamshire to Derbyshire. Thus the combined rates for *Northamptonshire, Leicestershire, Rutland*, and Soke of *Peterborough* are estimated to be $4{\cdot}91 \pm 1{\cdot}71$ per cent. in boys and $14{\cdot}29 \pm 2{\cdot}80$ per cent. in girls, the latter rate being significantly above 4 per cent.

South Pennine and West Northumberland areas (Nos. 4, 8). Passing north-east from Leicestershire, the adjoining areas of *Lincolnshire* give low rates, but to the north and north-west prevalence in the southern portion of *Nottinghamshire* is apparently high, but falls off in the low-lying parts of the county to the north. I have therefore regarded the North-East division as non-goitrous, and included the remaining divisions and Mansfield with the adjacent county of *Derbyshire*, where the rates based on twenty medical officers were $5{\cdot}15 \pm 1{\cdot}03$

Table XX.

Frequencies of Thyroid Enlargement found by Author in a Series of Schools by the Method of Categories. Also Frequencies based on the Mean Standard of the School Medical Officers of Somersetshire and Devonshire, and on the 42 mm. Limit.

Locality.	Girls. Total examined.	Girls. Mean Rates for Ages 11, 12, 13. Cat. 01. γ_1.	Cat. 2. γ_2.	Cat. 3. γ_3.	Calculated Goitre Rates based on Mean Standard of 20 M.O.'s.	Calculated Goitre Rates based on the 42 mm. Limit.*	Boys. Total examined.	Boys. Mean Rates for Ages 11, 12, 13. Cat. 01. γ_1.	Cat. 2. γ_2.	Cat. 3. γ_3.	Calculated Goitre Rates based on Mean Standard of 19 M.O.'s.	Calculated Goitre Rates based on the 42 mm. Limit.†
Devonshire:												
Crediton	—	—	—	—	—	—	54	0·418	0·527	0·055	0·502	0·334 ± 0·043
Ashburton	—	—	—	—	—	—	40	0·530	0·455	0·015	0·397	0·306 ± 0·039
Bovey Tracey	—	—	—	—	—	—	23					
Plympton	—	—	—	—	—	—	72	0·578	0·405	0·017	0·353	0·382 ± 0·039
Alphington	—	—	—	—	—	—	35	0·626	0·374	—	0·308	0·229 ± 0·048
Teignmouth	—	—	—	—	—	—	88	0·639	0·361	—	0·298	0·258 ± 0·031
Dawlish	—	—	—	—	—	—	55	0·688	0·298	0·014	0·254	0·224 ± 0·038
Okehampton	65	0·461	0·378	0 161	0·476	0·401 ± 0·041	71	0·603	0·297	—	0·239	0·228 ± 0·034
Tiverton	117	0·624	0·292	0·084	0·314	0·273 ± 0·028	154	0·664	0·225	0·011	0·185	0·185 ± 0·021
Exeter	126	0·657	0·286	0·057	0·280	0·233 ± 0·025	165	0·745	0·250	0·005	0·201	0·196 ± 0·021
Torquay	165	0·710	0·248	0·042	0·229	0·206 ± 0·021	171	0·827	0·173	—	0·126	0·139 ± 0·018
Plymouth	150	0·732	0·237	0·031	0·206	0·188 ± 0·022	164	0·826	0·174	—	0·127	0·140 ± 0·018
Barnstaple	132	0·752	0·200	0·048	0·189	0·183 ± 0·023	152	0·865	0·135	—	0·093	0·114 ± 0·017
Somersetshire:												
Taunton	119	0·655	0·287	0·058	0·282	0·245 ± 0·027	91	0·729	0·271	—	0·215	0·205 ± 0·029
Bridgwater	149	0·740	0·242	0·018	0·198	0·179 ± 0·021	150	0·777	0·223	—	0·172	0·173 ± 0·021
Bath	254	0·781	0·208	0·011	0·159	0·152 ± 0·015	242	0·917	0·080	0·003	0·050	0·083 ± 0·012

Surrey:												
Farnham	163	0·663	0·217	0·020	0·177	0·166 ± 0·020	156	0·792	0·208	—	0·158	0·163 ± 0·020
Denbighshire:												
Llanrwst, &c.	—	—	—	—	—	—	72	0·750	0·250	—	0·196	0·164 ± 0·029
Cheshire:												
†Knutsford	38	0·772	0·193	0·035	0·169	—	—	—	—	—	—	—
†Northwich	139	0·835	0·138	0·027	0·109	0·104 ± 0·017	—	—	—	—	—	—
†Stockton Heath, Lymm	58	0·885	0·098	0·017	0·060	0·066 ± 0·022	—	—	—	—	—	—
†Runcorn, Halton	105	0·893	0·079	0·028	0·054	0·085 ± 0·018	—	—	—	—	—	—
†Altrincham	94	0·903	0·072	0·025	0·044	0·057 ± 0·016	—	—	—	—	—	—
Stockport	196	—	—	—	0·203	0·191 ± 0·019	—	—	—	—	—	—

* Rates actually found in first 7 and last 5 groups of schools; calculated in others. Probable errors of sampling.

† In these schools a complete survey of the *normal* children was not made by the author, but the values of γ_1 have been estimated from the survey of the same schools made in 1924–5 by Dr. A. V. Stocks, whose personal equation was found not to differ appreciably from the author's.

per cent. in boys and $11{\cdot}87 \pm 1{\cdot}62$ per cent. in girls. These are significantly high, but it is surprising to find only moderate rates for this county, usually regarded as the principal endemic centre of goitre; the highest prevalence is probably about Belper, Basford, Heage, Ripley, Heanor, Hayfield, Chapel-en-le-Frith, and Glossop. The adjoining parts of the *West Riding* to the north-east have a low prevalence indicated, the mean rate for boys and girls in Wakefield, Leeds, Sheffield, and Pontefract divisions being 3·25 per cent.; the Pennine divisions of Skipton and Ilkley give a higher mean rate of 6·47 per cent., and these have been included in the Pennine area with Keighley and Todmorden, and also Hyde and Stalybridge belonging to Cheshire. In *Lancashire* there is also a significant difference between rates for the Pennine districts and those for the low-lying parts nearer the sea-coast. From the details given by Dr. Butterworth, County Medical Officer of Health, I have divided the County Council area into four divisions whose exact constitution is given in the definition of areas No. 4, 7, 10 above. For the Northern division, north of the Ribble, the recorded rates are low; for the Pennine division, between the Ribble and a line from Southport to Rochdale, and thence east of Manchester, the rates are $10{\cdot}76 \pm 2{\cdot}42$ per cent. in boys and $19{\cdot}97 \pm 3{\cdot}46$ per cent. in girls; for the districts of Kearsley, Prestwich, and Newton, in the south, the rates are 8·90 and 17·55 respectively, and for the rest of the south-west portion of the county $4{\cdot}64 \pm 1{\cdot}71$ and $11{\cdot}27 \pm 2{\cdot}75$ respectively. The Pennine division is continuous with the adjacent Pennine districts referred to above, but the available data leave it doubtful how far north this belt extends; returns from the North Riding give no evidence of it, but it reappears in the western districts of Durham and *Northumberland*. If the latter county be divided into a Western region embracing the Pennine and Cheviot valleys and an Easterly industrial and sea-coast region (see definition of areas 8 and 13), the rates of prevalence are notably different, as shown in Table XV. For *Durham* County a detailed distribution is not available, but in Dr. Eustace Hill's report for 1923 details are given for Weardale, which constitutes the Pennine portion of the county. Here the prevalence was very high and similar to the adjoining Tyne valley in Northumberland; thus Dr. M'Gonigle found 13 out of 70 boys aged 12, and 29 out of 83 girls, to be goitrous. I have assumed these totals to be the same in 1924 and to be included in the county total; combining them with West Northumberland we have rates of $10{\cdot}96 \pm 3{\cdot}15$ per cent. in boys and $26{\cdot}89 \pm 4{\cdot}72$ per cent. in girls, both significantly high. There is therefore no doubt of the existence of a region of high prevalence here, and probably it is continuous with the Pennine area farther south.

Cheshire and North Wales area (No. 7). For parts of *Cheshire* high rates were returned, as shown in Table XV. The Boroughs of Hyde, Stalybridge, Crewe, and Congleton also recorded high rates, as did Chester and Wallasey, but not Birkenhead. 'Mid' Cheshire adjoins areas to the south and east with low rates, whilst the north-east and south-west divisions are both continuous with areas giving high rates. The rates found by Dr. A. V. Stocks in several localities, standardized, are shown in Table XX, and also comparable rates found by myself at two schools in Stockport and in a group of schools in the County of Denbighshire. The rate of 12·94 per cent. for girls in North-East Cheshire would be equivalent to at least 8 per cent. by the mean observer's standard. I have therefore defined a region of moderately high prevalence extending from the Pennine region, involving Manchester ($15{\cdot}77 \pm 2{\cdot}20$ per cent. for girls), Stockport, the North-East, West, and South-West divisions of Cheshire, and two adjacent districts of Lancashire, the towns of Chester, Wallasey, Crewe, and Congleton, and the counties of Denbigh, Carnarvon, and Merioneth. The aggregate rates for this area are $7{\cdot}72 \pm 1{\cdot}57$ per cent. for boys and $16{\cdot}01 \pm 2{\cdot}37$ per cent. for girls.

Kent and Sussex area (No. 9). The Cranbrook district of *Kent* and the adjoining Borough of Tunbridge Wells have recorded rates of prevalence in girls of 28 per cent. and 19 per cent. respectively, as contrasted with 2 per cent. in the

rest of the county. The adjoining western portion of East *Sussex* has also a high mean rate for boys and girls, and combining these three areas we have $7{\cdot}24 \pm 3{\cdot}46$ per cent. in boys and $21{\cdot}32 \pm 5{\cdot}53$ per cent. in girls, the latter being significantly above 4 per cent. There is therefore here another region of high prevalence, possibly extending to the sea at Hastings and across the high ground in the south of Surrey.

Relation to Altitude and Geological Formation.

A relation between altitude above sea-level and goitre prevalence has been established in Switzerland,[27] where the maximum incidence seems to occur on both sides of the Alps in the zone between 500 and 1,000 metres. Such a relationship may not, however, be found to apply to the different climatic and geological conditions in England and Wales. The conclusions reached above do suggest that a relation to altitude may be looked for, since the 'goitre areas' marked out seem to favour the hilly regions. An effort has therefore been made to determine what correlation, if any, exists between altitude above sea-level and the prevalence of thyroid enlargement at age 12, as shown by the school medical officers' returns.

Rural areas. The country districts might be expected to be more sensitive to any effect of altitude than the towns. The difficulty which presents itself here is that whereas the altitude of a town can be easily measured within small limits, the populations of rural areas are scattered, and wide areas must therefore be taken as units in order to obtain rates, so we can only use some approximation to their average altitude.

In Table XV are five columns relating to the altitudes above sea-level of those county areas whose boundaries were definite enough to use as units. Using a large contoured map on which these boundaries had been marked out, a computation was made by means of small ruled squares of the amounts of area within the boundaries (i) below 250 ft., (ii) between 250 and 500 ft., (iii) between 500 and 1,000 ft., (iv) above 1,000 ft. These approximate measurements have been reduced to percentages of the total area, which are given in Table XV. In this way it was possible to obtain 62 county areas of England and Wales for correlation purposes, if the mean rates for boys and girls be used, or 53 if the separate rates be used.

In the first place an approximate measure of the mean altitude of each of these unit areas was arrived at by multiplying the 4 percentages by the corresponding central values of the altitude groups, taking these to be (i) 125 ft., (ii) 375 ft., (iii) 750 ft., (iv) 1,500 ft. The resulting 'mean altitudes' range up to 1,100 ft., and they are classified into twelve groups, indicated by Roman numerals in the fifth altitude column of Table XV; thus II means a mean altitude from 100 to 199 ft., III from 200 to 299 ft., and so on. For correlation with the thyroid rates, the actual mean altitudes were used as estimated, and the coefficients calculated by direct computation of product moments, weighting each thyroid rate

[27] See Reference No. 8.

with the square root of the number of medical officers concerned in it. This gives us:

Mean altitude 416 ft. Standard deviation 221 ft.

Aggregate goitre rates: for boys 4·52 per cent., girls 10·27 per cent.

Correlation between mean altitude and goitre rate in county districts. { Boys $r = 0{\cdot}1420 \pm 0{\cdot}0678$; Girls $r = 0{\cdot}1285 \pm 0{\cdot}0681$

There is therefore a small, but possibly significant, correlation with mean altitude.

The aggregate rates in girls for groups of areas with similar mean altitudes are given in Table XXI.

TABLE XXI.

Group as indicated in Table XV	II.	III–IV.	V–VI.	VII–VIII.	IX–XI.
Range of mean altitude (ft.)	100–	200–	400–	600–	800–
Total girls examined	11537	36836	12853	10417	1422
Total girls with enlarged thyroid	1005	3359	1205	1806	156
Number of medical officers	46	93	35	43	5
Aggregate thyroid rate	8·71 ± 1·04	9·12 ± 0·73	9·38 ± 1·09	17·34 ± 1·16	10·97 ± 2·94

The rate at altitudes from 600 to 800 ft. is certainly significantly higher than at lower altitudes, but the final group is too small to be sure whether the rate falls again above 800 ft.

When the mean goitre rate in boys and girls is correlated with the percentages of area lying within certain zones, the results are as follows:

With percentage of area above 250 ft. . .	$r = 0{\cdot}1563 \pm 0{\cdot}0836$.
„ „ „ „ between 250 and 500 ft.	$0{\cdot}0240 \pm 0{\cdot}0856$.
„ „ „ „ „ 500 and 1,000 ft.	$0{\cdot}1250 \pm 0{\cdot}0843$.
„ „ „ „ „ 250 and 1,000 ft.	$0{\cdot}1150 \pm 0{\cdot}0845$.

There is a suggestion here, but no proof, that the zone between 500 and 1,000 ft. is more important than the zone between 250 and 500 ft. in its influence on thyroid rates. This has been shown more effectively by dividing the districts in two ways as follows:

TABLE XXII.

	No. of M.O.'s.	Boys. Examined.	Boys. +	Boys. Rate.	Girls. Examined.	Girls. +	Girls. Rate.
Districts with less than ½ their area above 500 ft.	204	69185	2497	3·61 ± 0·31	68136	6301	9·25 ± 0·50
Districts with more than ½ their area above 500 ft.	18	5415	873	16·12 ± 1·46	5198	1230	23·66 ± 1·88
Districts with less than ½ their area above 250 ft.	79	29922	1266	4·23 ± 0·50	29449	2910	9·88 ± 0·80
Districts with more than ½ their area above 250 ft.	143	44678	2104	4·71 ± 0·38	43885	4621	10·53 ± 0·60
Districts with less than ½ their area at 250–1,000 ft.	102	40045	1971	4·92 ± 0·45	37807	3887	10·28 ± 0·71
Districts with more than ½ their area at 250–1,000 ft.	120	34555	1399	4·05 ± 0·40	34527	3644	10·55 ± 0·65

The differences between the first pair are considerable and significant, whilst those between the second and third pairs are negligible.

Towns. In Tables XVI and XVII the altitude above sea-level of each urban district, borough, and county borough, for which separate thyroid rates are obtainable, is indicated by means of four groups as follows:

A = situated on the sea-coast or on an estuary.
B = „ inland and below 250 ft.
C = „ „ „ between 250 ft. and 500 ft.
D = „ „ „ above 500 ft.

Treating these as qualitative groups in a continuous normal distribution, the result of correlating the altitude with thyroid rates in boys and girls is:

For 133 boroughs and urban districts	With boys' rate, $r = 0{\cdot}2416 \pm 0{\cdot}0551$.
	„ girls' rate, $r = 0{\cdot}2814 \pm 0{\cdot}0539$.
For 73 county boroughs	With boys' rate, $r = -0{\cdot}0058 \pm 0{\cdot}0789$.
	„ girls' rate, $r = -0{\cdot}0321 \pm 0{\cdot}0789$.

This seems to indicate a definite relation with altitude for the smaller towns, but none whatever for the larger towns. This result might be expected if goitre frequency were a function of the altitude from which the water-supply is derived, rather than the altitude at which the people are living, for the larger towns usually draw their water-supply from a distance.

The mean thyroid rates for the groups are as follows:

TABLE XXIII.

	Small Towns.			Large Towns.		
	No.	Boys' Rate.	Girls' Rate.	No.	Boys' Rate.	Girls' Rate.
Group A	38	1·76	4·00	28	1·89	5·35
B	47	2·32	6·74	30	1·66	5·00
C and D	48	4·18	9·37	15	1·56	4·86

The *proximity of hills* to towns might be expected to have some relation to the rates of thyroid enlargement, if there is anything in the old theory that deep valleys favour goitre. This relation has been examined by measuring the approximate distance in miles from each town to the nearest points on three contour lines, namely the 250 ft. line, the 500 ft. line, and the 1,000 ft. line, when the town lies below the altitude in question. The towns have then been separated into groups based on these distances, and the thyroid rate for girls in the aggregate population of each group has been calculated with its probable error.

These figures indicate that for small towns, whether below 250 ft. or between 250 and 500 ft., close proximity to the 500 ft. zone probably favours higher rates, though the differences do not exceed about twice their probable errors; for large towns no such relation is indicated. For low-lying large towns it appears that proximity of mountain or moorland over 1,000 ft. in altitude favours high rates, but there is no such relation for small towns, nor for any towns in the 250–500 ft. zone. The results of this analysis are therefore rather indefinite and conflicting.

TABLE XXIV.

		No. of Girls examined.	Thyroid enlarged.	No. of M.O.'s.	Aggregate Rate for Group.
Towns below 250 ft.					
Small towns	1–3 miles from 500 ft. line	3608	233	22	6·46 ± 1·38
	4–6 " " " "	5649	395	22	6·99 ± 1·39
	7 or more miles from 500 ft. line	12509	536	51	4·28 ± 0·95
Small towns	1–10 miles from 1,000 ft. line	2850	192	12	6·74 ± 1·88
	11 or more miles from 1,000 ft. line	18916	972	83	5·14 ± 0·70
County boroughs	1–3 miles from 500 ft. line	6919	181	16	2·62 ± 1·57
	4–6 " " " "	15535	747	39	4·81 ± 1·02
	7 or more miles from 500 ft. line	29652	1486	96	5·01 ± 0·65
County boroughs	1–10 miles from 1,000 ft. line	8910	918	27	10·33 ± 1·29
	11 or more miles from 1,000 ft. line	43196	1496	124	3·46 ± 0·57
Towns at 250–500 ft.					
Small towns	1 mile from 500 ft. line	4970	459	22	9·23 ± 1·42
	2 or more miles from 500 ft. line	5955	357	16	6·33 ± 1·66
Small towns	1–4 miles from 1,000 ft. line	3135	214	13	6·62 ± 1·80
	5 or more miles from 1,000 ft. line	7790	622	25	7·98 ± 1·32
County boroughs	1 mile from 500 ft. line	9509	409	23	4·30 ± 1·30
	2 or more miles from 500 ft. line	3266	171	6	5·24 ± 2·62
County boroughs	1–4 miles from 1,000 ft. line	7130	306	18	4·29 ± 1·50
	5 or more miles from 1,000 ft. line	5645	274	11	4·85 ± 1·93

Geology. Much has been written about the influence of geological formation upon goitre frequency, and it is not proposed in this paper to do more than touch upon this aspect. The large probable errors in the data, in any case, render a detailed analysis on this basis difficult and of doubtful value. Moreover the ages of the strata immediately underlying a district are probably of less importance in their influence on water supplies than the kind of subsoil overlying them, and the classification of subsoils would be a task of some magnitude. In the present paper I have merely classified the county areas in Table XV according to the predominant geological formation outcropping in each area, using the term 'predominant' to refer to the fraction of the total area occupied by such formation on a geological map.

The following broad grouping has been used and the aggregate thyroid rates for the groups of rural areas so defined are as given below. The key to the areas included in each group will be found in the column 'Geology' in Table XV.

TABLE XXV.

Geological Formation predominant in the Areas concerned.	No. of M.O.'s.	Boys. Examined.	Boys. +	Boys. Rate.	Girls. Examined.	Girls. +	Girls. Rate.
(a) Cambrian, Ordovician, or Silurian	15	6565	149	$2·27 \pm 1·08$	6627	440	$6·03 \pm 1·78$
(b) Devonian and Old Red Sandstone	17	5940	730	$12·29 \pm 1·37$	5599	1181	$21·09 \pm 1·51$
(c) Carboniferous limestone and Millstone grit	27	5054	268	$5·32 \pm 0·89$	4905	647	$13·19 \pm 1·41$
(d) Coal Measures	28	13163	297	$2·25 \pm 0·79$	10160	693	$6·82 \pm 1·31$
(e) Triassic (and Permian) formations	33	14024	1011	$7·21 \pm 0·85$	14150	2189	$15·47 \pm 1·30$
(f) Lias and Oolite	36	8863	303	$3·42 \pm 0·74$	8569	960	$11·23 \pm 1·20$
(g) Chalk or Greensand	57	21422	618	$2·88 \pm 0·56$	20916	1523	$7·28 \pm 0·92$
(h) Recent formations	19	4454	31	$0·70 \pm 0·90$	4295	88	$2·05 \pm 1·52$

The highest rates in the above table are given by the Devonian and Old Red Sandstone group, but this is due to the inclusion of a single district, that of West Somerset, where the rates recorded were phenomenally high. If this district be omitted the rates for the remainder of this group are $2·46 \pm 1·05$ in boys and $10·34 \pm 1·79$ in girls. The Trias group and the Carboniferous limestone and Millstone grit groups give undoubtedly the most uniformly big rates, both in boys and girls, the aggregate rates being significantly high for both groups. The Lias and Oolite formations of the Jurassic system come next, with a rate significantly above 7 per cent. in girls, but not significantly high in boys. It is noteworthy that the chalk on the whole is not associated with high rates, though there are exceptions, such as Hampshire and the Isle of Wight. The Coal Measures are not characterized by high rates except in Mid-Lancashire, and in local patches in Somerset and Northumberland, at Ebbw Vale, and perhaps in some parts of Durham. A classification of local rates in Somerset according to geological strata was made by Dr. W. G. Savage, the County Medical Officer of Health, in his report for 1924; if the rates for the separate medical officers given on page 9 of that report be reduced to a common standard by means of their known personal equations and combined, the resulting mean rates are: Coal Measures 31·6, Lias and Oolite 22·7, Trias 21·8, Carboniferous limestone 20·5.

The general conclusion seems to be that country areas underlain by the Trias, Carboniferous limestone, or Old Red Sandstone tend to have high rates of thyroid enlargement in England and Wales. That the connexion is due to the nature of the water-supply percolating through these rocks can scarcely be doubted, but whether Fellenberg's recent observations in Switzerland that fossiliferous Jurassic rocks were rich in iodine, whilst certain Triassic limestones were poor in iodine, will prove to have any bearing on this, it is not possible to say at present. I would refer in this connexion, however, to the careful work of Hercus, Benson, and Carter [28] on the iodine content of soils and rocks in New Zealand, which

[28] See Reference No. 11.

seem to have some correlation with the conclusions here reached. They find, broadly speaking, that iodine is relatively abundant in the soils from igneous rocks, except in siliceous volcanic rocks; in marine limestones it is usually small in amount, though not invariably; in soils derived from marine sandstones and greensands there is a low iodine content unless carbonaceous or fossiliferous matter is abundant. It seems conceivable that the chalk formations in this country might be found to contain more iodine than the Carboniferous limestones owing to their high fossiliferous content, and that the coal formations and tertiary deposits might be found relatively rich in iodine.

It is impossible in this paper to go farther into this question, but I suggest that an analysis of soils and rocks in this country for iodine content by the method described by Hercus, Benson, and Carter would be a useful biochemical research.

Conclusions.

1. Comparison of goitre rates based on methods of visual estimation without measurement is proved to be of very limited value owing to the large personal equation involved.

2. In the returns from the thyroid survey by some 600 school medical officers on 375,000 children aged 12 in 1924, this difficulty was so apparent that no reliable conclusions could be drawn from them until the probable errors due to personal equation had been computed by means of a sampling survey of 3,000 children in company with twenty of the medical officers concerned. By application of frequency curves obtained by actual measurement of the gland, the range of error due to personal differences of opinion was calculated in terms of thyroid breadth and approximate formulae for the probable errors in the official returns were arrived at.

3. The use of a standard 42 mm. gauge for thyroid breadth to define a point at which enlargement of the gland may be deemed to commence in boys and girls aged 10–13 is recommended for future comparative work, since by this means the personal equation would be so largely reduced as to make reliable comparisons between the results of different observers possible.

4. It seems probable from such data as are at present available that up to a certain point all degrees of thyroid enlargement increase in prevalence in roughly the same proportions in passing from non-goitrous to goitrous districts, which suggests that so-called 'physiological' goitres differ from endemic goitre only in degree.

5. Examination of geographical distribution in the light of the estimated probable errors indicated that:

(*a*) Goitre is more prevalent in girls than boys, but the sex ratio falls rapidly from about five in areas almost free from goitre to two where prevalence in boys is about 10 per cent., and then gradually to unity for regions of high prevalence.

(*b*) Urbanization is associated with lower goitre incidence than in rural areas in regions where goitre prevalence is above the normal.

(*c*) Towns on the sea-coast tend to have lower rates than inland towns, but this effect is confined to the immediate coast and is subject to exceptions.

(*d*) High incidence is found in a belt extending from Cornwall north-eastwards through Somerset and between the Cotswold and Chiltern Hills into Northamptonshire, thence northwards to Derbyshire and up the Pennine chain. Offshoots extend from Wiltshire to the Isle of Wight, across Hereford and South Wales, and across Cheshire and North Wales, whilst another small area is found in part of Kent and Sussex.

(*e*) It seems probable that in the eastern and south-eastern Midland counties and a number of large towns, incidence would be practically zero if measured by the 42 mm. standard, though by the standard of the average medical officer a residual rate of about 3 or 4 per cent. in girls and ½ to 1 per cent. in boys is usually present.

6. Altitude above sea-level has a slight relation to prevalence in rural areas and small towns, the zone between 500 and 1,000 ft. being apparently most favourable to goitre. Rates tend to be highest where the Devonian and Triassic formations or Carboniferous limestone are outcropping.

7. In view of the conclusions reached in this and three other papers [29] it would seem that prophylactic administration of iodine to girls in some endemic areas of England and Wales might be desirable.

[29] See References Nos. 1, 3, 12.

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THE CIRCULATION RATE IN SOME PATHOLOGICAL STATES, WITH OBSERVATIONS ON THE EFFECT OF DIGITALIS[1]

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THE essential function of the heart is to act as a pump, and the efficiency of a pump is gauged by its output per unit of time. That cardiac efficiency has not been investigated clinically along these lines to any great extent is due to the difficulties inherent in most methods of measuring cardiac output. Methods such as those of Krogh and Lindhard (1), Christiansen, Douglas, and Haldane (2), Meakins and Davies (3), Burwell and Robinson (4), or Field, Bock, Gildea, and Lathrop (5), require the subject to be trained in complicated respiratory manœuvres. Many subjects indeed, especially dyspnoeic cardiac patients, are unable to carry out these manœuvres.

In the more recently introduced ethyl-iodide method of Henderson and Haggard (6) previous training of the subject is unnecessary. Mobitz (7), Cullis, Rendel, and Dahl (8), Davies and Gilchrist (9), Rosen and White (10), and Starr and Gamble (11) have already made use of this method in investigating the circulation of healthy individuals, and Mobitz (7) has also employed it in the study of the circulation rate in disease. With the exception of Starr and Gamble (11) these investigators express themselves as satisfied with the validity of the method.

In some hands the circulation rates indicated by this method in healthy subjects are rather higher than those given by previous methods, resting values up to 10 litres a minute being obtained. The results of Davies and Gilchrist (9), however, range between 4·5 and 8 litres for normal individuals lying at rest, and therefore approximate those obtained by methods based on the Fick principle.

Apparatus and Technique employed.

The apparatus used was that described by Davies and Gilchrist, and the various modifications in the original technique suggested by them were adopted. The oxygen absorption as well as the circulation rate was measured at each

[1] Received September 5, 1927.

[2] A grant was made by the Moray Fund of Edinburgh University towards the expenses of the work.

determination. Oxygen absorption divided by circulation rate gives the arterio-venous oxygen difference or oxygen utilization. The stroke volume was in every case calculated from the actual heart-rate and not from the pulse-rate.

The determinations were for the most part done on patients lying in bed. As the spirometer with its attachments was too cumbrous to be moved about a ward, it was kept in an adjacent side-room, and patients whose circulation rate was to be estimated were wheeled to it in their beds. In the few ambulant cases investigated the determinations were done with the patient lying on a couch after he had been resting for thirty minutes. Most of the investigations were made between 9–11 a.m., two to four hours after the patient's breakfast. It was not found feasible to do the estimations with the patients fasting except in the exophthalmic goitres and myxoedemas, the latter cases being examined immediately after routine basal metabolic rate estimations. Thus by having the patients at rest lying, and as far as possible in the same state as regards food, an endeavour has been made to secure uniform conditions throughout the series of cases. In dyspnoeic cardiac patients a completely recumbent position was usually not possible, and these patients were kept in the more comfortable propped-up position, the same position being assumed at each examination.

TABLE I.

Average Results from Cases of Aortic Incompetence and of Mitral Stenosis.

Case.	Heart-rate.	Circ. Rate. Litres per Min.	Stroke Volume. c.c.	Art.-ven. O_2 diff. Vol. %.	Lesion.
Mrs. F. D.	76	6·9	91	4·33	Aortic incompetence
R. N.	79	5·2	65	5·82	
W. R.	69	7·9	114	2·85	
M. McD.	99	6·15	62·5	4·85	
D. C.	37·5	4·25	114	6·07	
J. D.	98	2·4	25	8·43	
K. G.	91	5·0	55	5·17	Mitral stenosis
F. K.	81	7·04	88	3·6	
E. B.	98	5·45	56	4·16	

Discussion of Results.

The findings in 163 determinations on 24 patients have been tabulated. In the smaller tables to be found throughout the text *average* results are given. The patients investigated comprise cases of cardiac disease, anaemia, exophthalmic goitre, and myxoedema. Possibly the most interesting are the cases of cardiac disease, and here information as to the effect on the circulation of valvular lesions, complete heart-block, cardiac failure, and of the administration of digitalis has been obtained.

Valvular lesions. Six cases with *aortic incompetence* were examined, and in four of them the circulation rate was within normal limits, while in two it was low. In one of the latter (D. C.), whose circulation rate, 4·25 litres per minute, was somewhat low, there was the complication of a complete heart-block.

This is especially interesting in view of the old clinical teaching that a rapid heart-rate is of advantage in aortic incompetence as tending to lessen regurgitation by shortening diastole. The apparent support given to this statement by these results is modified by the fact that the circulation rate maintained at rest, though low according to the somewhat arbitrary standards adopted, was yet apparently sufficient for the patient's needs. This individual showed little circulatory distress even on moderate exertion. In the other case (J. D.) the circulation rate was definitely low and remained between 2 and 3 litres while she was under observation. This patient showed no clinical improvement under treatment and eventually died. At post-mortem the myocardium was extremely flabby, while the aortic valve was both incompetent and stenotic. In view of the condition of the myocardium, the low circulation rate, the cardiac failure, and the subsequent death of the patient cannot be attributed entirely to the actual valvular lesion. Meakins and Davies (12) and Mobitz (7), in cases of aortic incompetence, as occurs in the uncomplicated cases here, found that the circulation rate was not appreciably affected.

Three cases of mitral stenosis were examined, and they also gave circulation rates within ordinary limits, although in two this was only maintained by a rapid heart-rate, the output per beat being small. This differs from the results obtained by Meakins, Dautrebande, and Fetter (13) and by Mobitz (7), who found a definite diminution in both circulation rate and stroke volume in cases of mitral stenosis. In none of the cases here reported, however, was the stenosis clinically very marked, being the result presumably of an endocarditis of fairly recent origin, while in those other cases, certainly those of Meakins, Dautrebande, and Fetter, the lesions were much more advanced.

In such a case as Mrs. D. the low circulation rate which she at times showed was obviously not directly caused by the *incompetence* of her mitral valve. It increased on the adoption of measures which, though they might increase the power of the myocardium, were unlikely to affect the condition of the valve.

From these results it would appear that of valvular lesions, aortic incompetence and early mitral stenosis do not affect appreciably the rate of blood-flow provided that the myocardium is functioning efficiently.

Arrhythmias. Although three cases of *auricular fibrillation* were investigated, unfortunately it was not possible in any of them to compare the circulation rate during fibrillation and normal rhythm. Of the three cases, two were observed when there were no marked signs of cardiac failure and when the heart was not under the influence of digitalis. The average circulation rates in those two cases were 4·7 and 5·4 litres per minute, the stroke volumes being relatively small, 50 and 52 c.c. As there was little or no pulse deficit during the period in question, this has not entered into the production of the low stroke volume.

Two of the cases, Mrs. S. and J. H., were observed when the ventricular rate was very rapid (200 per minute in Mrs. S.), and in each this state was associated with a low circulation rate and definite cardiac failure. It would appear probable, on the analogy of the decrease in cardiac output shown by

Stewart, Crawford, and Hastings (14) to occur in healthy dogs during experimental irregular tachycardia, that the irregular tachycardia in these two cases is in itself partly responsible for the low circulation rate. A possible element of myocardial weakness must, however, be taken into account also. The gradual decline in the circulation rate in J. H. towards the end of the period she was under observation was not associated with any marked tachycardia, and was almost certainly due to failing myocardial power.

In J. D., after the administration of digitalis, pulsus bigeminus developed. Three determinations were made while the pulse was bigeminal, and a fourth after normal rhythm had been restored. No significant change in circulation rate was noted, on passing from one condition to the other. Apparently, therefore, during bigeminy the presumably deficient output of the extra-systole is counterbalanced by an increased output at the normal beat. At one period the rhythm in this case was liable to change frequently from bigeminy to normal rhythm and vice versa, and from counts made at these change-overs it was determined that no change in the heart-rate occurred. This is consistent with the observation that the assumption of bigeminal rhythm has no effect on the cardiac output.

Complete heart-block. Three cases of complete heart-block were examined, and in each the stroke volume, as one would expect, was large. In two the circulation was being maintained at a value sufficient to enable the patient to go about in comfort, the actual rates being 4·3 and 5·5 litres. The ventricular rate in these two varied between 36 and 40 per minute. The third patient, who had the remarkably slow ventricular rate of 21 per minute, was cyanotic and was easily rendered dyspnoeic. His circulation rate was only 3·2 litres per minute, and this despite a stroke volume of 151 c.c. Henderson and Prince (15), from measurements of the pericardial capacity in the cadaver, estimated the maximum stroke volume at 230 c.c. In this case, even with the output per beat at a maximum, a circulation rate of 4·8 litres could not be exceeded at the ventricular rate obtaining.

TABLE II.

Average Results from Determinations done during Periods of Definite Cardiac Failure.

Case.	Heart-rate.	Circ. Rate. Litres per min.	Stroke Volume. c.c.	Art.-ven. O_2 diff. Vol. %.
Mrs. D.	100	2·57	26	13·64
Mrs. S.	200 ±	3·6	18	7·82
J. H.	149 ±	3·05	20·5	8·34
J. D.	98	2·4	25	8·43
J. B.	21	3·2	151	7·78

Cardiac failure. Those cases in this series showing definite sign of cardiac failure in the resting state without exception had low circulation rates (Table II) when the failure was marked. Three of these cases (Mrs. D., Mrs. S., and J. H.) improved clinically, and coincident with the improvement there was an increase in circulation rate. As compared with the circulation rates in other patients with cardiac lesions who were examined, those in the cases with marked cardiac

failure are definitely low. In this group also the stroke volumes are lower (except in J. B., who had complete heart-block) and the oxygen utilization is higher than in the others.

Meakins and Davies (16) also found the circulation rate to be low in cardiac failure, and the actual results reported by them correspond closely in magnitude with those in this series.

The circulation rate is the product of the heart-rate and the output per beat, and it is obvious, the heart-rate being rapid, that the low circulation rate in all but one of these cases is due to a deficient output per beat. It has already been shown that valvular lesions play little *direct* part in reducing stroke volume, so that the small stroke volume and consequent low circulation rate must be due to myocardial failure. In cases of auricular fibrillation there is, in addition to the insufficient contractile power of the myocardium, the further handicap of the rapid irregular rhythm.

A contrast to these cases is presented by J. B., who had complete heart-block. In him also there was a low circulation rate associated with definite clinical signs of cardiac insufficiency, but his stroke volume was large, 151 c.c., the low circulation rate being due to the extraordinarily slow ventricular rate. This, however, cannot be a common mechanism in the production of the low circulation rate in cardiac failure.

The first four cases in Table II, and those reported by Meakins and Davies, are representative of the commoner types of cardiac failure. In them the circulation rate was low, apparently as a result of the failure of the myocardium to maintain a sufficient output per beat, rapid irregular tachycardia being a possible contributory factor in cases of auricular fibrillation.

The effect of digitalis on the circulation rate. In six of the cardiac patients opportunity was taken to study the effect of digitalis on the circulation rate. The digitalis was given as the powdered leaf according to the formula of Eggleston (0·015 grm. per lb. body-weight), the dose being fractioned into three or sometimes more parts, and given over twelve to twenty-four hours. There was often more or less marked nausea and vomiting after and sometimes during the administration. When this occurred there is a possibility that the full effect may be masked through loss of some of the digitalis or by changes in circulation consequent on nausea and vomiting. Only a few observations appeared to have been affected by such factors, and the results from these have been discarded.

In Table III the average heart-rate, circulation rate, and stroke volume, before and for one week after the various doses of digitalis, are given and compared. Sufficient determinations have been made to render the averages reliable. Of these eleven doses, six caused a definite increase in circulation rate, three did not affect it, and two decreased it. Four of the doses which caused an increase were given to Mrs. D., and one each to Mrs. S. and J. H. Mrs. D., before the first three of these doses, had a low circulation rate and definite signs of cardiac insufficiency. When the last dose which caused an increase was given the circulation rate was being maintained at a

higher level, and signs of insufficiency, though still present, were not so marked. The doses causing an increase in Mrs. S. and J. H. were both given in the presence of a low circulation rate and very definite signs of cardiac failure. The

TABLE III.

Average Results before and after Digitalis.

	Before Digitalis.			After Digitalis.			% Change.		
Case.	H. R.	C. R.	S. V.	H. R.	C. R.	S. V.	H. R.	C. R.	S. V.
Mrs. D.	100	2·57	26	70·3	3·17	45	−29·7	+23	+73
	93	2·88	31	72·3	3·57	49	−22	+24	+58
	91	3·33	36·3	62	5·1	83	−32	+53	+128
	80·7	5·37	67	74·3	3·8	51·3	− 8	−29	−23
	80	4·75	59·5	79·5	7·1	90·5	− 1	+49	+52
Mrs. S.	200	3·6	18·3	104	6·47	65·3	−48	+80	+257
J. H.	96	4·7	49	91	4·4	49·5	− 5	− 6	+ 1
	149	3·05	20·5	82	4·2	51	−45	+38	+149
J. D.	98	2·43	24·7	83	2·45	29·5	−15	+ 1	+19
Mrs. T.	105	5·37	51·7	68·3	4·1	60·3	−35	−24	+17
T. McN.	100·3	5·13	51·3	89·3	5·03	56·3	−11	− 2	+11

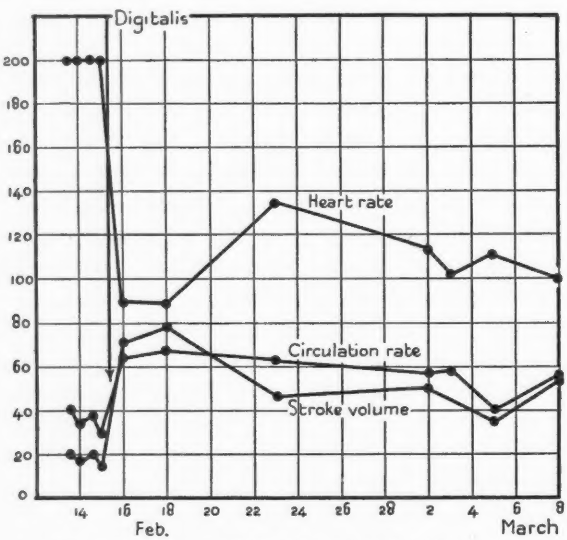

CHART I. Effect of digitalis (Mrs. S.).
Circulation rate in litres per minute. Stroke volume in c.c.

extent of the increase which occurred in Mrs. S. is well shown in Chart I. Two of the doses which had no effect on the circulation rate were given while the patients had no very definite signs of cardiac failure and a moderate circulation rate. In the case of J. D. the circulation rate was low and insufficiency definite, and the drug, besides causing no increase in the circulation rate, produced no improvement in the patient's condition. One of the doses apparently causing a decrease was given to Mrs. D., and it is doubtful whether the fall in cardiac output can be ascribed to the digitalis. This dose of digitalis was given on March 2. The circulation rate, which had been considerably raised by the preceding dose of digitalis, fell steadily from February 26 to March 6, the digitalis

producing no appreciable effect. Subsequently the circulation rate proceeded to increase gradually up to the time of giving the next dose on March 22. Why this dose of digitalis produced no appreciable effect on the circulation rate when the others given to the same patient all did is not clear. It was certainly absorbed, for a definite increase in the P–R interval was noted after it. The other dose causing a decrease in circulation rate was given to Mrs. T., a case of slow fibrillation, and here the decrease appears to be due to the drug.

The circulation rate then may be increased, decreased, or unaffected by digitalis, different effects occurring not only in different patients but also in the same patient at different times. An increase appears most likely to occur where there are signs of cardiac insufficiency and a low circulation rate, but in such cases does not invariably occur. When signs of failure are little marked or absent and the circulation rate is not definitely low, an increase seems unlikely, the circulation rate usually remaining unaltered or diminishing.

Since digitalis diminishes the heart-rate, increase in circulation rate, when it occurs, must be due to increase in stroke volume, i.e. to increase in the contractile power of the myocardium. This increase in stroke volume apparently occurs only, or at least most markedly, in cases where the myocardium is inefficient, little or no effect being produced if the heart-muscle is functioning satisfactorily. In cases such as J. D. where, despite obvious myocardial failure and a low output per beat, digitalis causes no increase in stroke volume or circulation rate, presumably the damage to the heart muscle is such as to render it incapable of stimulation.

In auricular fibrillation, however, with a rapidly contracting ventricle slowing the heart-rate would tend to increase the output per minute. Possibly this explains why, clinically, digitalis is most efficacious in cases of auricular fibrillation. In these cases the slowing of the ventricular rate and the increase in the contractile power of the myocardium both tend to increase the circulation rate, while in cases with normal rhythm these two actions of digitalis are antagonistic in their effects on cardiac output. This antagonism of these two actions of digitalis appears to be the explanation of the variability of its effect on the circulation rate.

With the action of digitalis what it is, the method by which it produces improvement in cases of cardiac failure is obvious. It raises the low circulation rate to which the signs and symptoms of cardiac failure presumably are due. This, the obvious explanation of the improvement resulting from digitalis in cardiac failure, has from time to time had doubt thrown upon it by writers who have applied results obtained in healthy animals to disease in man.

Anaemias. An increase in the rate of blood-flow appears the logical compensation for the decreased oxygen-carrying power of the blood in anaemia. A number of observers, including Dautrebande (17), Harrison and Blalock (18), Lundsgaard (19), and Harrop (20), have described an increase in circulation rate in the presence of severe anaemia. Mobitz (7), however, using the ethyl-iodide method, was unable to demonstrate any definite increase in this condition.

In the three cases of anaemia here examined there is no definite evidence of any compensatory increase in circulation rate. When the haemoglobin was at its lowest, the circulation rate was in none of them specially high, and in one case only did it show any tendency to decrease as the haemoglobin increased.

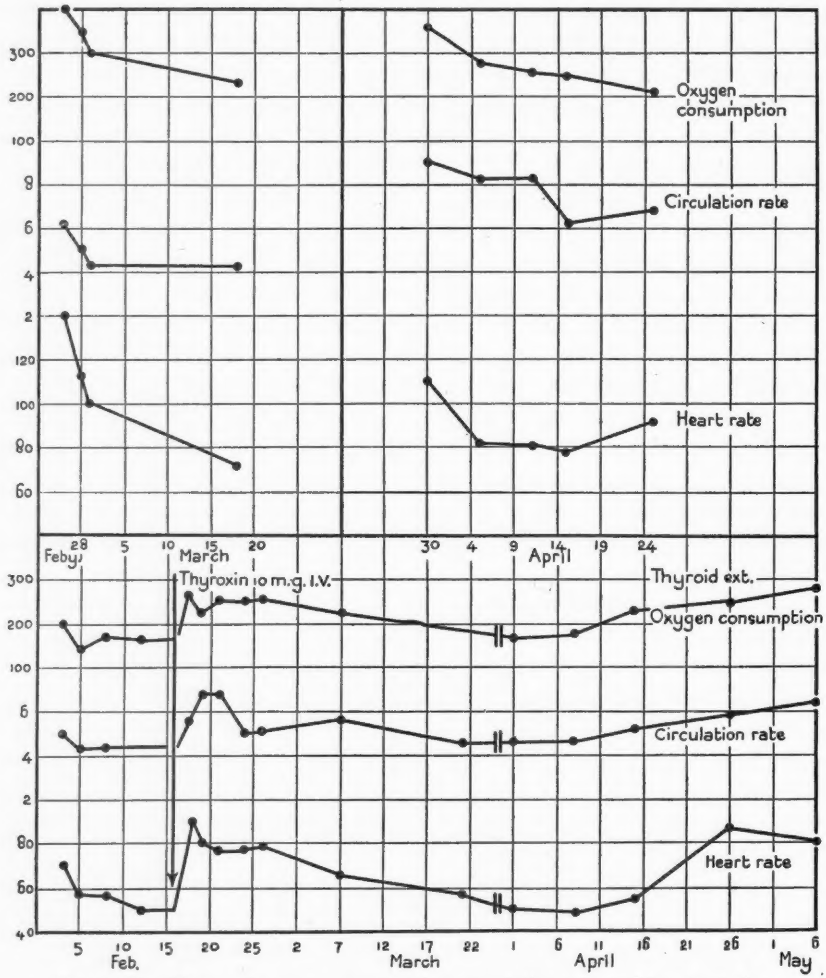

Chart II. Changes in oxygen consumption, circulation rate, and heart-rate in cases of exophthalmic goitre and myxoedema.

Indeed, in Mrs. K. there was a definite increase in circulation rate towards the end of the period of observation when the haemoglobin had increased considerably.

A possible fallacy, which may explain this failure of the ethyl-iodide method to demonstrate any increase in circulation rate in cases of anaemia, exists in the determinations done on these cases. The coefficient of solubility of ethyl iodide in anaemic blood may be less than that in blood with 100 per cent. Hb. This, of course, would make the figure obtained lower than the actual rate of blood-flow.

Hyperthyroidism and myxoedema. Three cases of exophthalmic goitre and two of myxoedema were investigated. In the exophthalmic goitres the circulation rates tended to be high, as in the cases previously reported by Davies, Meakins, and Sands (21) and by Liljestrand and Stenstrom (22), while in the myxoedemas it was definitely low. An even more interesting point is the parallelism which exists between the circulation rate and the oxygen consumption in individual cases.

Three cases, two goitres and a myxoedema, showed definite variations in metabolism, and in each this parallelism is to some extent present. This can be

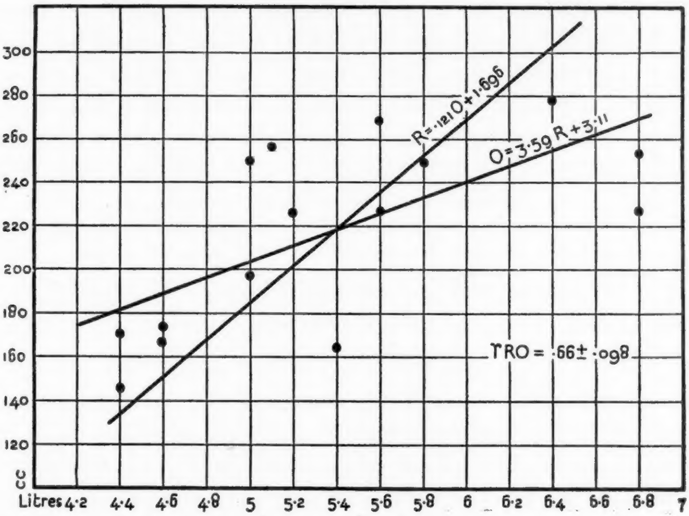

CHART III. Abscissa, circulation rate (R). Ordinate, oxygen consumption (O). Results from Mrs. McC.

seen in Chart II, being most evident in Mrs. McC., on whom a fairly extensive series of determinations was made, the changes in metabolism resultant on treatment offering special facilities for the study of this point. A further consideration of the figures from this case shows that the coefficient of correlation between circulation rate and oxygen absorption is $0{\cdot}66 \pm 0{\cdot}98$, which indicates a high degree of parallelism between these two functions. The extent of this correlation is further shown in Chart III.

The correlation between circulation rate and oxygen absorption, though definite, is incomplete. A complete correlation is not to be expected, for the oxygen utilization is also a variable factor.

Summary.

163 determinations of the circulation rate have been made by the ethyl-iodide method on twenty-four patients suffering from various cardiac lesions, from anaemia, from myxoedema, and from exophthalmic goitre. The results of these determinations indicate that:

1. Of valvular lesions, aortic incompetence and early mitral stenosis do not directly affect the circulation rate.

2. In a case of pulsus bigeminus resulting from digitalis the bigeminal rhythm did not affect the cardiac output.

3. In complete heart-block the output at each beat is large.

4. In cardiac failure the circulation rate is low, this being due in ordinary types to a failure of the myocardium to maintain a sufficient output per beat, with, in cases of auricular fibrillation, rapid irregular tachycardia a possible contributory factor.

5. The circulation rate may be increased, decreased, or unaffected by digitalis, different effects occurring not only in different patients but also in the same patient at different times. An increase appears most likely to occur when there are signs of cardiac insufficiency and a low circulation rate, but in such cases does not invariably occur. When signs of failure are absent or little marked and the circulation rate is not definitely low, an increase is less likely, the circulation rate usually remaining unaltered or decreasing.

6. In cases of anaemia no definite changes in circulation rate attributable to the anaemia were observed.

7. In exophthalmic goitre the circulation rate tends to be high, and in myxoedema low. A high degree of correlation appears to exist between circulation rate and oxygen absorption.

I have to thank Professor Edwin Bramwell and Dr. W. T. Ritchie for permission to investigate patients from their wards. It gives me special pleasure to express my thanks to Professor D. M. Lyon, in whose wards most of the patients were, for the facilities extended, and for his advice and encouragement.

Summary of Case Histories.

Mrs. D. Cardiac failure; mitral incompetence with ? stenosis. Aged 32. Cook. No children. Complaints: palpitation, especially at nights, for three and a half years; dyspnoea on exertion for two and a half years; occasional oedema of ankles for six to eight months. Previous health: miscarriages seven and eight years ago. Acute rheumatism two years ago: no other rheumatic history. Wassermann reaction negative. Admitted 27.4.26. Moderate cardiac failure with oedema. Pulse regular. Blood-pressure 140–150/90–100. Heart enlarged. $\frac{111}{1''/7''}$ in sixth left space. Blowing mitral systolic murmur propagated into axilla. Same systolic murmur audible in all other areas. No diastolic or presystolic murmur in any area. Second sound accentuated in pulmonary area. Treatment: rest in bed; digitalis. Discharged 1.6.26. Readmitted 20.11.26. Marked dyspnoea and cyanosis on exertion. Slight oedema. Physical examination and treatment as before. Discharged at own request 14.12.26. Readmitted 10.1.27, having collapsed in street. Praecordial pain and palpitation. Slight oedema only. Physical examination and treatment as before. Discharged 14.5.27. Electrocardiogram: normal rhythm; slight increase in P–R interval. After digitalis marked increase in P–R interval, and after one dose sino-auricular block. No evidence of ventricular preponderance.

Mrs. S. Auricular fibrillation; cardiac failure. Aged 55. Housewife. Five children. Complaints: extreme breathlessness on exertion; oedema of

ankles at night; and gastric symptoms. Several years' duration. Previous health: no history of acute rheumatism or scarlet fever. Appearance suggestive of past hyperthyroidism. Wassermann reaction —. Admitted 12.2.27. Pulse-rate about 100–120, extremely irregular. Actual heart-rate uncountable, but pulse deficit large, probably 80–100. Marked venous pulsation in neck. Heart dilated, $\frac{111}{1''/5''}$ in fifth left space. No bruits detected even when heart-rate slowed. No oedema. Electrocardiogram: auricular fibrillation; ventricular rate 200 per minute before first dose of digitalis. Treatment: rest in bed and digitalis.

J. H. Auricular fibrillation; chronic bronchitis and emphysema. Female, unmarried. Aged 63. Cook. Complaints: dyspnoea, palpitation, and occasional pain on exertion; occasional oedema of ankles—twelve months' duration. Previous health: acute rheumatism three years ago; occasional sore throats when younger; chronic winter cough for some years—worst during past winter. Admitted 19.2.27 with acute bronchitis. Irregular pulse with pulse deficit on admission which disappeared after two to three days' rest in bed. Heart $\frac{111}{1''/4\frac{1}{2}''}$ in fifth space. No bruits audible. Electrocardiogram: auricular fibrillation. Readmitted. Extremely distressed, cyanosed, orthopnoeic. Heart-rate $150\pm$ fibrillating: pulse deficit $50\pm$.

J. D. Aortic stenosis and incompetence. Female, aged 16. At home. During past eight weeks attacks of praecordial pain on exertion and during night. Attacks of breathlessness during night. Cough, and on one occasion small haemoptysis. Scarlet fever aged 8. No other illnesses. Wassermann reaction —. Pulse regular. Blood-pressure 90/60. Heart enlarged, $\frac{111}{1''/5''}$ in sixth space. No thrills. Mitral area: systolic murmur prop. into axilla. Diastolic murmur occasionally audible. Aortic area: rough systolic murmurs prop. into neck. No diastolic heard. Electrocardiogram: pulsus bigeminus after digitalis. Treatment: rest in bed, digitalis. 1.7.27 died. Post-mortem: aortic stenosis and incompetence. No disease of mitral valve. No recent vegetations. Myocardium extremely flabby.

Mrs. T. Auricular fibrillation; carcinoma corporis uteri. Aged 68. Housewife. Two children. Complaints: pain and frequency of micturition; vaginal discharge (carcinoma of body of uterus). No symptoms relative to circulatory system. No rheumatic history. Wassermann reaction —. Pulse totally irregular: little or no pulse deficit. Heart not enlarged. No bruits. Second sound reduplicated in all areas. Electrocardiogram: auricular fibrillation. Form of ventricular complexes suggestive of an arborization block. Treatment: rest in bed, digitalis; transferred for radium therapy.

T. McN. Chronic bronchitis and emphysema; myocarditis. Male, aged 61. Labourer. Ex-soldier. Complaints: cough, increasing shortness of breath on exertion; twelve months' duration. Previous history: fairly frequent bronchitis. Wassermann reaction —. Before and on admission very numerous extra-systoles which cleared after a few days in bed. Arterial wall thickened and tortuous. Blood-pressure 140/80. Heart $\frac{111}{\frac{1}{2}''/3''}$ in fifth left space. Mitral systolic bruit. Electrocardiogram: extra-systoles, auricular in origin.

K. G. Mitral stenosis and incompetence. Rheumatic carditis. Female, aged 17. Shop assistant. Previous health: chorea four years ago. Wassermann reaction —. Admitted 3.6.26 with chorea. Mitral systolic and presystolic murmurs with accentuated pulmonary second sound. Heart not enlarged. Developed pericarditis while in ward. Discharged 14.9.26. Readmitted 31.12.26 for rest and observation. Cardiac condition as on first admission.

F. K. Mitral stenosis and incompetence. Rheumatic carditis. Female, aged 24. Typist. Previous health: acute rheumatism and pericarditis aged 13; pneumonia followed by heart-block aged 14. Wassermann reaction —. Admitted 29.12.26, having been in bed at home six months following an attack of acute rheumatism; occasional praecordial pain and palpitation even in bed. Pulse rapid, 90–100. Regular. Heart enlarged $\frac{111}{1''/6''}$ in fifth left space. Loud blowing systolic murmur in mitral area prop. into axilla. Pulmonary second reduplicated. Electrocardiographic examination: increase in P–R interval; this greatly exaggerated after digitalis.

E. B. Rheumatic carditis. Mitral stenosis and incompetence. Female, aged 16. Domestic servant. Previous health: nil of note. Admitted 30.10.26 with acute rheumatism. Developed pericarditis while in ward, and also a pleurisy. Joint pains showed tendency to become subacute. Pulse regular. Blood-pressure 110/80. Heart $\frac{111}{\frac{1}{2}''/4\frac{1}{2}''}$ in fifth space. Mitral area: systolic murmur prop. into axilla. Definite mid diastolic murmur. Pulmonary second sound accentuated.

Mrs. F. D. Aortic incompetence (rheumatic). Aged 22. Housewife. One child. Previous health: frequent sore throats, tonsils large and septic. Wassermann reaction —. Palpitation and breathlessness moderately easily induced by exertion for five years past, and this more marked since child born nine months ago. Now again $3\frac{1}{2}$ months pregnant. Pulse: large excursion. Blood-pressure 140/60. Heart not enlarged, $\frac{111}{\frac{1}{2}''/3\frac{1}{2}''}$ in fifth left space. Systolic and diastolic bruits originating in aortic area. Electrocardiogram: nil abnormal showing.

R. N. Aortic incompetence. Syphilitic aortitis. Male, aged 49. Carter. Admitted with complaint of abdominal pain. No definite circulatory symptoms. Wassermann reaction + + +. Pulse: Corrigan. Blood-pressure 140/40. Heart enlarged, $\frac{111}{\frac{1}{2}''/4''}$ in sixth space. Systolic and diastolic aortic murmurs.

W. R. Aortic incompetence. Syphilitic aortitis. Male, aged 57. Packer. Previous health: Wassermann reaction + + +. Symptoms: breathlessness and occasional praecordial pain on exertion for twelve months. Occasional oedema of feet for six months. Looked anaemic. Pulse: Corrigan. Blood-pressure 130/35. Heart enlarged, $\frac{111}{\frac{1}{2}''/5\frac{1}{2}''}$ in sixth left space. Systolic and diastolic murmurs originating in aortic area. Electrocardiogram: definite left-sided preponderance.

M. McD. Aortic aneurysm. Aortic incompetence. Male, aged 30. Miner. Admitted 10.12.25 complaining of pain in chest, hoarseness, and dyspnoea on exertion. Wassermann reaction +. Pulses equal and synchronous. Blood-pressure 120/60. Well-marked pulsation second right intercostal space. Heart $\frac{111}{1\frac{1}{4}''/4''}$ in fifth left space. Aortic systolic and diastolic murmurs. Increase in transverse dullness across manubrium. Readmitted. Same physical signs and symptoms. Electrocardiogram: normal rhythm. Left ventricular preponderance.

D. C. Complete heart-block. Aortic incompetence. Male, aged 64. Warehouseman. Previous health: syphilis 39 years ago. Wassermann reaction —. Breathless only on moderate exertion. No cardiac pain. No fits. No oedema. Pulse-rate 36, Corrigan. Blood-pressure 240/60. Heart enlarged, $\frac{111}{\frac{3}{4}''/5\frac{1}{2}''}$ in sixth left space. Aortic systolic and diastolic murmurs. Electrocardiogram: complete dissociation of auricular and ventricular complexes.

G. J. Complete heart-block. Male, aged 45. Railway guard. Previous history: nil of note. Wassermann reaction —. Complaints: attacks of giddiness.

No oedema. No marked dyspnoea on exertion. Pulse-rate 36. Heart not enlarged, $\frac{111}{\frac{1}{2}''/3\frac{3}{4}''}$ in fifth left space. Sounds closed all areas. Electrocardiogram: complete dissociation of auricular and ventricular complexes.

J. B. Complete heart-block. Male, aged 68. Rubber worker. 'Giddy turns', occasionally associated with loss of consciousness, repeatedly during last two years. Increasing breathlessness on exertion for two years. No oedema. History of gonorrhoea at age of 18. Wassermann reaction –. Cyanotic tinge in lips. Pulse extremely slow—21 per minute—regular. Blood-pressure 205/95. Heart $\frac{111}{1''/4\frac{3}{4}''}$ in fifth left space. Heart-rate 21 per minute. Mitral systolic murmur propagated towards axilla. Other sounds closed. Electrocardiogram: complete heart-block. Left-sided ventricular preponderance.

Mrs. K. Secondary anaemia. Aged 32. Housewife. One child aged 5. 'Bloodless' since aged 18–20. Headaches, breathlessness, palpitation, and gastric disturbance. Anaemia of secondary type with very low colour index. Cause not ascertained. Heart not enlarged. Haemic murmurs. Bruit de diable.

J. L. Secondary anaemia. Male, aged 24. Clerk. Marked anaemia of secondary type of apparently about three years' duration. Causal factors not discovered. Heart not enlarged. Haemic murmurs all areas. Bruit de diable.

M. S. Pernicious anaemia. Male, aged 66. Progressive weakness, swelling of feet and ankles for thirteen months. Yellowish tinge. Dark pigmented patches on buccal mucosa and skin of legs. Blood-pressure 100–120/50–60. Heart $\frac{11}{\frac{1}{2}''/4''}$ in fifth left space. No bruits, first mitral impure. Complete achlorhydria. No X-ray evidence of gastric carcinoma. Wassermann reaction –. Colour index 1·1 to 1·3. Film suggestive of pernicious anaemia.

E. H. Exophthalmic goitre. Female, aged 16. Between-maid. Nervousness, loss of weight, and amenorrhoea for eight months. Goitre and exophthalmos noticed for two months only. Moderate uniform enlargement of thyroid; pulsatile, systolic bruit. Pulse regular. Heart not enlarged. Systolic murmurs all areas. Marked degree of hyperthyroidism on admission, settled down quickly with rest in bed and Lugol's iodine min. x t. i. d. Transferred for operation. B.M.R. + 74 per cent.– + 19 per cent.

A. S. Exophthalmic goitre. Female, aged 26. Single. 'Nerves', goitre and slight exophthalmos for one year. Moderate uniform enlargement of thyroid with a systolic bruit over it. Heart not enlarged. Systolic murmurs all areas. On admission mild but definite hyperthyroidism. Settled quickly with rest in bed and Lugol's iodine min. v t. i. d. B.M.R. + 37 per cent.– + 12 per cent.

Mrs. W. Exophthalmic goitre. Aged 51. Housewife. Admitted 9.5.27. Goitre and hyperthyroid symptoms noted for nine weeks before admission. Moderate uniform enlargement of thyroid. Usual eye signs present, also exophthalmos. Heart $\frac{11}{1''/4\frac{1}{2}''}$ in sixth space. Systolic bruit all areas. Rhythm regular. Rest in bed; Lugol's iodine. Little improvement. B.M.R. + 65 per cent. on 13.5.27.

Mrs. McC. Myxoedema. Aged 45. Housewife. Eight children. Transferred from surgical ward after operation for ventral hernia. (Stitch abscess during first few days in ward.) Obvious myxoedema. Heart not enlarged. Blowing systolic murmurs all areas. B.M.R. – 40– + 22 per cent.

Mrs. S. V. Myxoedema. Aged 61. Housewife. Fourteen children. Five miscarriages. Typical major myxoedema. In hospital on various occasions during past four years. Heart not enlarged; no murmurs; mitral first sound faint. B.M.R. – 44 per cent.– – 11 per cent.

Case.	Date.	Heart-rate.	Circulation Rate. Litres per min.	Stroke Volume. c c.	Resp. Minute Volume. Litres.	Oxygen Consumption. c.c. per min.	Art.-ven. O_2 diff. Vol. %.	Alv. CO_2 %.	Remarks.
Mrs. D., aged 32. Wt. 59–51 kg. Mitral incompetence. Cardiac failure.	2.12.26	102	2·7	27	13·35	324	11·99	3·27	Orthopnoea, some oedema.
		102	2·5	24	14·1	382	15·29	3·26	
	4.12.26	96	2·5	27	14·4	—	—	—	
	5.12.26	Digitalis 1·7 grm. in 3 doses							Nausea—no vomiting.
	6.12.26	71	3·0	43	9·05	303	10·1	3·8	
		66	3·3	49	9·05	279	8·46	3·7	
	8.12.26	74	3·2	43	9·7	294	9·19	—	
	10.1.27	Readmitted – Cardiac failure							
	12.1.27	Digitalis 1·7 grm. in 3 doses							Vomited part of first dose.
	13.1.27	75	4·8	63	7·54	—	—	—	10 a.m.
		62	3·2	52	6·91	216	6·8	4·33	2.30 p.m. Nausea.
	17.1.27	90	4·1	45	10·19	—	—	—	
	18.1.27	85	4·5	54	10·81	316	7·1	4·11	
	25.1.27	93	2·6	28	10·84	—	—	—	
		89	3·0	34	9·54	267	8·9	3·64	
	26.1.27	98	2·8	28	10·83	—	—	—	
		92	3·1	34	9·83	248	8·0	3·48	
	27.1.27	Digitalis 1·8 grm. in 7 doses at 6 hourly intervals							Marked nausea and vomiting.
	28.1.27	69	3·6	51	8·87	254	7·06	4·66	
	29.1.27	66	3·6	54	8·71	260	7·2	4·05	
	1.2.27	82	3·5	42	12·13	—	—	3·76	
	7.2.27	98	3·4	34	10·64	—	—	3·93	
	8.2.27	84	3·4	40	9·67	378	11·12	—	
	11.2.27	100	4·3	43	10·6	378	8·79	4·02	Excited.
	14.2.27	91	3·1	35	8·38	285	8·9	4·19	
	14.2.27	Digitalis 1·7 grm. in 3 doses							Marked nausea after last dose. Vomited once.
	16.2.27	59 ±	5·6	95	7·37	252	4·5	3·57	Dropping beats. Sino-auricular block.
	18.2.27	65	4·6	71	9·68	289	6·28	3·96	
	26.2.27	76	6·1	80	10·2	310	5·0	4·32	
	28.2.27	85	5.4	64	10·5	348	6·44	4·53	
	1.3.27	81	4·6	57	9·08	239	5·02	4·43	
	2.3.27	Digitalis 1·7 grm. in 3 doses							Nausea and vomiting.

	4.3.27	83	3·8	46	7·98	235	6·02	4·39	
	5.3.27	68	3·5	51	7·64	287	8·02	4·14	
	9.3.27	72	4·1	57	9·72	—	—	4·42	
	11.3.27	75	4·8	64	9·72	—	—	4·68	
	21.3.27	82	4·5	55	9·3	—	—	4·44	
	22.3.27	78	5·0	64	9·4	316	6·32	4·33	
	22.3.27	Digitalis 1·3 grm. in 5 doses							No nausea or vomiting.
	24.3.27	71	7·3	102	8·8	312	4·28	4·58	
	26.3.27	88	6·9	79	9·04	—	—	4·76	
	6.4.27	90	4·8	53	9·51	—	—	4·35	
	11.4.27	90	4·7	52	10·48	290	6·17	—	
Mrs. S., aged 55. Wt. 36 kg. Auricular fibrillation. Cardiac failure.	14.2.27	200	4·1	21	8·15	279	6·80	—	Very restless. Heart-rate from electrocardiogram. Uncountable otherwise.
		200	3·5	18	8·39	288	8·20	4·11	
	15.2.27	200	3·8	19	7·91	308	8·10	4·14	
		200	3·0	15	7·34	245	8·17	4·12	
	15–16.2.27	Digitalis 1·2 grm. in 3 doses							No nausea or vomiting.
	16.2.27	90	6·4	71	6·34	240	3·75	3·98	
	18.2.27	88	6·7	78	5·86	241	3·60	4·68	
	23.2.27	135	6·3	47	6·03	240	3·81	4·8	
	2 3.27	114	5·7	50	6·66	251	4·40	4·7	
	3.3.27	103	5·8	57	7·39	282	4·86	—	
	5.3.27	111	4·0	36	6·86	248	6·2	5·02	Not feeling well. Breathless.
	8.3.27	101	5·5	54	6·69	—	—	4·97	
J. H., aged 63, female. Wt. 73·5 kg. Auricular fibrillation.	22.2 27	102	4·8	47	7·67	269	5·60	4·43	
	23.2.27	95	4·6	49	7·37	252	5·48	4·16	
	26.2.27	90	4·6	51	8·18	286	6·22	4·37	
	10–11.3.27	Digitalis 2·4 grm. in 3 doses							Excessive nausea and vomiting.
	10.3.27	103	4·2	40	7·32	—	—	4·48	
	16.3.27	79	4·6	59	7·02	—	—	—	
	18.4.27	—	Readmitted.	Cardiac failure					
	19.4 27	140	2·5	18	9·45	250	10·0	3·81	Orthopnoea.
	20.4.27	157	3·6	23	12·39	240	6·67	3·46	Very distressed. Slightly cyanosed.
	20–21.4.27	Digitalis 1·8 grm. in 5 doses							No nausea or vomiting.
	22.4.27	80	4·3	54	7·75	174	4·05	3·63	
	23.4.27	84	4·1	48	9·68	264	6·44	3·6	
	3.5.27	95	3·9	41	8·42	268	6·87	3·54	
	8.5.27	101	3·7	37	7·66	257	6·95	4·09	
	12.5.27	110	3·5	31	7·9	261	7·46	3·97	

Case.	Date.	Heart-rate.	Circulation Rate. Litres per min.	Stroke Volume. c.c.	Resp. Minute Volume. Litres.	Oxygen Consumption. c.c. per min.	Art-ven. O_2 diff. Vol. %.	Alv. CO_2 %.	Remarks.
J. D., aged 16, female, Wt. 35·5 kg. Aortic stenosis and incompetence. Cardiac failure.	18.4.27	103	3·0	29	8·65	257	8·57	3·8	Heart-rate increased by excitement.
	19.4.27	97	2·1	21	7·22	183	8·71	4·41	
	20.4.27	94	2·2	24	7·11	176	8·00	3·88	
	21–22.4.27	Digitalis 1·1 grm. in 5 doses							No nausea or vomiting.
	23.4.27	82	2·5	30	6·68	176	7·04	4·32	Bigeminy.
	25.4.27	83	2·2	26	6·6	176	8·00	4·44	"
	27.4.27	84	2·9	35	7·03	236	8·14	4·52	"
	30.4.27	83	2·2	27	6·55	221	10·05	4·16	Regular rhythm.
Mrs. T., aged 68. Wt. 67·5 kg. Auricular fibrillation.	1.3.27	108	5·8	54	6·86	272	4·68	4·28	
	2.3.27	95	5·3	56	5·97	219	4·13	4·3	
	3.3.27	112	5·0	45	6·84	263	5·26	4·76	
	3–4.3.27	Digitalis 2·2 grm. in 3 doses							Nausea and vomiting after last dose.
	4.3.27	74	3·4	46	5·73	234	6·88	4·76	
	7.3.27	62	3·9	63	5·37	230	5·90	5·26	
	10.3.27	69	5·0	72	6·05	—	—	5·06	
T. McN., aged 61, male. Wt. 56 kg. Myocarditis.	30.3.27	90	4·7	52	9·34	281	5·98	4·67	Ocasional extra-systole.
	1.4.27	110	5·4	49	11·95	314	5·81	4·69	
	4.4.27	101	5·3	53	11·6	296	5·58	4·65	
	5–6.4.27	Digitalis 1·8 grm. in 5 doses							No nausea or vomiting.
	6.4.27	95	5·6	58	9·58	—	—	4·84	
	8.4.27	91	3·9	43	9·23	255	6·54	—	
	12.4.27	82	5·6	68	9·43	257	4·59	4·17	
K. G., aged 17, female. Wt. 61 kg. Mitral stenosis and incompetence.	18.1.27	92	4·9	53	6·84	272	5·55	5·19	
	28.1.27	90	5·1	56	6·60	244	4·78	5·55	
F. K., aged 24, female, Wt. 51·5 kg. Mitral stenosis and incompetence.	23.2.27	73	7·5	103	7·73	279	3·72	—	
	24.2.27	73	7·7	105	6·15	213	2·77	5·4	
	5.3.27	75	6·4	85	6·45	275	4·30	4·79	
	9.3.27	89	6·7	75	6·43	—	—	5·1	
	17.3.27	97	6·9	70	4·89	—	—	—	

E. B., aged 16, female. Wt. 41·8 kg. Mitral stenosis and incompetence.	4.2.27	100	5·4	54	6·23	211	3·91	5·05	
	22.2.27	95	5·5	57	5·06	242	4·40	—	
Mrs. F. D., aged 22. Wt. 44·5 kg. Aortic incompetence.	10.2.27	74	6·6	89	5·89	300	4·55	4·84	
	16.2.27	78	7·2	93	5·88	296	4·11	5·93	
R. N., aged 49, male. Wt. 68 kg. Aortic incompetence.	29.3.27	82	6·2	75	10·35	295	4·76	4·41	30 minutes' rest on couch.
		82	5·8	70	8·15	—	—	5·06	,, ,, ,,
	31.3.27	76	4·6	60	9·23	285	6·20	4·48	,, ,, ,,
		76	4·3	57	8·63	280	6·51	4·66	,, ,, ,,
W. R., aged 57, male. Wt. 53 kg. Aortic incompetence.	14.4.27	68	7·7	113	6·20	229	2·97	4·98	30 minutes' rest on couch.
	28.4.27	71	8·2	116	6·42	243	2·95	4·89	,, ,, ,,
		69	7·8	113	5·39	204	2·62	4·26	,, ,, ,,
M. McD., aged 30, male. Wt. 46 kg. Aortic incompetence. Aortic aneurism.	30.4.27	94	6·2	66	7·61	282	4·55	4·52	
	4.5 27	104	6·1	59	9·80	314	5·15	4·49	
D. C., aged 64, male. Wt. 73 kg. Complete heart-block. Aortic incompetence.	10.1.27	39	4·4	113	8·75	—	—	—	
		36	4·1	115	7·20	249	6·07	4·62	
G. J., aged 45, male. Wt. 50·5 kg. Complete heart-block.	7.1.27	36	5·5	154	8·28	277	5·04	5·16	
J. B., aged 68, male. Complete heart-block. Cardiac failure.	26.5.27	21	3·2	151	7·65	249	7·78	4·25	
									% Hb.
Mrs. K., aged 32. Wt. 57·2-65·8 kg. Secondary anaemia.	8.2.27	78	7·2	93	6·85	248	3·44	—	20
	10.2.27	76	6·8	89	6·15	236	3·47	4·68	26
	16.2.27	76	7 5	99	5·97	264	3·52	4·28	30
	24.2.27	71	7·1	101	5·46	233	3·28	4·52	36
	3.3.27	67	7·1	106	5·19	249	3·51	4·78	40

Case.	Date.	Heart-rate.	Circulation Rate. Litres per min.	Stroke Volume. c.c.	Resp. Minute Volume. Litres.	Oxygen Consumption. c.c. per min.	Art. Ven. O_2 diff. Vol. %.	Alv. CO_2 %.	% Hb.	Remarks.
	23.3.27	78	6·5	84	6·15	286	4·40	5·08	40	On couch, 30 min. rest.
	26.3.27	72	7·2	100	5·3	257	3·57	5·47	—	" "
	9.4.27	77	10·1	130	6·37	245	2·43	—	46	" "
	15.4.27	75	10·9	145	6·58	256	2·35	5·35	46	In bed. Noisy valve.
	23.4.27	66	9·2	139	5·60	244	2·65	5·25	54	On couch.
	27.4.27	68	9·7	143	5·39	243	2·51	5·23	56	" "
	11.5.27	68	8·9	131	5·67	247	2·78	5·17	60	In bed.
J. L., aged 24, male. Wt. 51 kg. Secondary anaemia.	4.3.27	89	7·7	86	7·1	327	4·24	4·69	20	
	17.3.27	79	7·3	92	7·41	—	—	4·79	30	
	31.3.27	67	6·2	93	5·79	255	4·11	5·18	40	
	9.4.27	89	7·0	79	6·62	264	3·77	5·21	36	
	21.4.27	68	7·6	111	6·35	260	3·42	5·46	50	
	30.4.27	77	6·5	85	6·20	280	4·31	5·22	46	
	4.5.27	73	7·4	101	6·74	291	3·93	5·5	—	
M. S., aged 66, male. Wt. 55·5 kg. Pernicious anaemia.	15.2.27	70	6·2	88	9·47	—	—	4·34	38	
	21.2.27	73	6·4	88	9·28	216	3·38	—	45	
	26.2.27	66	5·4	82	9·29	295	5·46	4·0	54	
	4.3.27	58	5·2	90	6·46	238	4·58	4·87	64	
	16.3.27	68	3·9	58	8·13	—	—	—	60	
	6.4.27	61	4·0	65	6·65	220	5·5	5·27	70	
	22.4.27	71	5·5	77	7·94	276	5·0	5·28	70	
	13.5.27	67	5·0	75	8·53	298	5·96	5·17	64	
E. H., aged 16, female. Wt. 40·5–45·5 kg. Exophthalmic goitre.	26.2.27	140	6·2	44	7·79	402	6·48	5·32		
	28.2.27	112	5·1	45	7·60	349	6·84	4·33		
	1.3.27	100	4·3	43	7·40	304	7·07	4·27		
	18.3.27	72	4·3	59	5·93	234	5·44	4·77		
A. S., aged 26, female. Wt. 48·5 kg. Exophthalmic goitre.	30.3.27	110	9·0	82	8·75	357	3·96	4·96		
	5.4.27	82	8·2	98	5·11	275	3·35	4·84		
	11.4.27	80	8·2	102	5·19	256	3·12	5·29		
	15.4.27	78	6·2	80	5·15	244	3·94	5·29		
	25.4.27	91	6·8	75	4·77	210	3·09	5·29		

Mrs. W., aged 51. Wt. 44·5 kg. Exophthalmic goitre.	11.5.27	134	7·1	53	8·56	331	4·66	4·37	
	13.5.27	125	7·2	57	9·33	370	5·16	4·22	
	18.5.27	110	7·8	71	8·1	371	4·78	4·33	
Mrs. McC., aged 45. Wt. 80–70·8 kg. Myxoedema.	3.2.27	71	5·0	71	4·47	197	3·94	4·36	
	5.2.27	58	4·4	75	4·46	146	3·32	3·85	
	8.2.27	57	4·4	77	4·43	171	3·89	—	
	12.3.27	50	5·4	108	4·14	165	3·06	4·27	
	16.2.27	Thyroxin 10 mg. intravenously							
	18.2.27	90	5·6	63	6·05	269	4·8	4·23	
	19.2.27	81	6·8	84	5·17	227	3·34	4·42	
	21.2.27	77	6·8	88	5·89	253	3·72	4·60	
	24.2.27	77	5·0	66	5·97	251	5·02	4·42	
	26.2.27	79	5·1	64	5·85	257	5·04	4·26	
	7.3.27	65	5·6	86	5·32	227	4·05	4·31	
	21.3.27	57	4·6	81	5·16	—	—	4·50	
	1.4.27	50	4·6	93	5·12	167	3·63	4·04	28.3.27. Thyroxin 10 mg. by mouth.
	8.4.27	49	4·6	95	4·80	174	3·78	4·67	
	15.4.27	56	5·2	95	5·45	227	4·37	4·39	13.4.27. Ext. thyr. gr. iii t. i. d.
	26.4.27	87	5·8	67	6·50	249	4·27	4·83	
	6.5.27	81	6·4	79	6·48	278	4·34	4·52	
Mrs. S. V., aged 61. Wt. 68 kg. Myxoedema.	18.3.27	57	3·7	64	4·18	160	4·32	4·84	
	23.3.27	54	4·1	76	3·34	143	3·49	3·96	22.3.27. Thyroxin 10 mg. by mouth.
	1.4.27	50	3·0	60	3·99	152	5·06	4·69	
	8.4.27	61	3·5	58	5·03	164	4·11	4·54	6.4.27. Thyroxin 10 mg. by mouth.
	12.4.27	58	3·1	54	5·18	190	6·13	4·89	
	26.4.27	69	3·7	54	6·75	184	4·97	4·63	22.4.27. Ext. thyr. gr. iii t. i. d.

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THE BLOOD CHOLESTEROL IN NEPHRITIS[1]

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Introduction.

WITHIN the last few years a great deal of work has been done upon the cholesterol content of the blood in a large number of different diseases. This work has recently been reviewed by Campbell (1) in this Journal, and a striking feature of his summary is the discrepancy in the results recorded in certain conditions by different observers. In addition, it is made clear that our knowledge of the metabolism of cholesterol in the healthy organism, its origin, its function, and its ultimate fate, is as yet rudimentary.

Amongst the groups of cases summarized in the review already quoted, there were records of cases of nephritis, in some of which the results were mutually contradictory. In acute nephritis Kahn (2) has reported a series of six cases, in all of which the blood cholesterol was normal. In chronic parenchymatous nephritis a marked increase in the blood cholesterol has been found by Epstein and Rothschild (3), Chauffard, Laroche, and Grigaut (4), and other workers (5, 6, 7). Klinkert (8) has reported eight cases in which cholesterol was increased, and although most were of the chronic interstitial type, two at least were diagnosed as parenchymatous. Kahn (2), on the other hand, found normal figures in the majority of twenty-three cases quoted, while Henes (9) finds it increased in all cases of 'chronic nephritis', although he agrees with Epstein and Rothschild (3) that it falls with the onset of uraemia. Bennett and Dodds (10) state that an increased cholesterol content of the blood is a feature of cases of nephrosis, in sharp contrast with cases where uraemia and cardio-vascular changes dominate the picture, in which the blood cholesterol is usually found to be normal. With regard to chronic interstitial nephritis, Klinkert (8) found an increased cholesterol value in a few cases, whereas Kahn (2) found it normal in the majority of his series.

It will be seen, from the results quoted above, that there is a fairly general agreement that the blood cholesterol is increased in chronic parenchymatous nephritis. In acute nephritis only six cases are quoted, and in chronic interstitial nephritis the results showed a considerable degree of variation.

This section of Campbell's review concludes with the summary: 'Evidently more work is needed to be certain of the exact conditions under which the blood

[1] Received September 17, 1927.

cholesterol is increased in nephritis, but there is general agreement that it is likely to be increased in cases of chronic parenchymatous and chronic interstitial nephritis, especially the former, and that it often falls as uraemia develops.'

In view of this lack of certainty as to the exact conditions under which the blood cholesterol deviates from the normal in nephritis, it was decided to investigate a series of cases of all types of kidney disease, in order to discover whether consistent results could be obtained. But, as the investigation proceeded, it became clear that those cases which showed constantly increased blood cholesterol figures would furnish the most fruitful field for study, and attention was therefore concentrated upon the groups of patients suffering from acute and chronic parenchymatous nephritis. In certain of these patients the changes occurring in the cholesterol content of the blood were followed at frequent intervals over a period of weeks or months in an attempt to learn something more of the pathology of the condition. Although this latter object was not achieved, some points of interest were observed, the chief being the prognostic significance of the alterations in the cholesterol content of the blood during the course of the disease in cases of parenchymatous nephritis.

Altogether a total of 181 cases have been investigated over a period of eighteen months. For purposes of subsequent discussion these cases are divided into groups, and the main features of each group are expressed in the form of a table. These groups are divided as follows: acute nephritis, both active and quiescent, twenty-two cases; chronic parenchymatous nephritis, thirty cases; chronic interstitial nephritis and arteriosclerosis, thirty-four cases. Toxaemias of pregnancy, sixteen cases; and uraemia, twenty-four cases. Of the uraemic cases, ten are discussed under other headings, so that the actual number of cases reviewed in this report is 116. The majority of the remaining cases, not accounted for under the above headings, were 'surgical' cases, while in a few instances there was some complicating factor which vitiated the results, with the consequence that such cases were of necessity discarded.

The actual cholesterol estimations were performed on oxalated blood-plasma, in every instance using the colorimetric chloroform extraction method of Grigaut (11), following the technique developed by Myers and Wardell (12). A modification of this method was recently fully described in this Journal by MacAdam and Shiskin (13), and their description has been the basis of the technique employed in this investigation.

The method selected, although simple, rapid, and accurate, for small quantities of plasma, is admittedly less accurate than the digitonin method of Windaus (14), which is the most reliable method known at present. The chief objection to the digitonin method is the rather large quantity of blood required, which renders it unsuitable for a clinical investigation. It is stated by Gardner (15) that the Wardell and Myers technique is accurate within 5 per cent. if due precautions be observed, as against an accuracy within 2 per cent. using Windaus's method. In view of the facts stated above, all results are quoted to two places of decimals only, as the third figure conveys nothing when this method is employed.

The alcohol and ether extraction method of Bloor (16) yields rather higher results, but does not appear to be so widely used in this country as the Wardell and Myers method. It was not employed at all in this series of cases, so that no opinion can be expressed as to the relative accuracy of the two methods. It has been suggested that the standard solution of cholesterol in chloroform used for purposes of comparison in the colorimeter could, with advantage, be replaced by a standard solution of naphthol green B. The use of this artificial standard was attempted for a short time, but it was quickly abandoned, as the results obtained were quite unreliable when controlled against the standard solution of cholesterol in chloroform.

Before considering the results obtained in nephritis, it is necessary to consider briefly the normal cholesterol content of the blood, as well as a few of the factors, both physiological and pathological, which exercise an influence upon the blood cholesterol. It is clear that full allowance must be made for such factors in interpreting results, and that, when their influence might possibly vitiate the results, such cases must be excluded from a general consideration of the subject of nephritis.

A short series of ten normal individuals was first investigated. The maximum and minimum values found in the plasma were 0·20 and 0·13 grm. per cent. with an average of 0·17 per cent. These results agree well with those of Campbell (17), MacAdam and Shiskin (13), Chauffard, Laroche, and Grigaut (4), and other observers (18, 19), as well as with those of Klinkert (8), whose results are valuable because they were controlled by the more accurate digitonin method. These figures are therefore accepted as the limits of normal variation.

A seasonal variation in the blood cholesterol has been described by Currie (20), the average values being much higher in the summer than in the winter. This work needs confirmation; in one healthy man examined at monthly intervals over a period of one year, the maximum and minimum figures obtained were 0·16 and 0·18 per cent., and in this paper seasonal variation as a factor will be ignored.

Of the physiological factors causing an increase in the blood cholesterol, pregnancy (4, 21) and the premenstrual phase of the menstrual cycle (22) are the most important. For this reason a separate series of pregnant cases will be discussed. It should also be stated that, as a routine, blood was not collected from female patients during the premenstrual phase.

A diet which has a high fat content is definitely capable of increasing the cholesterol content of the blood (19, 23, 24), but the length of time which has elapsed since the meal is important, as the cholesterol increase occurs later than the increase of fat and lecithin (25), and indeed may be overlooked on this account. Paradoxically enough, starvation is also often associated with a raised blood cholesterol (26). In nearly all the cases the blood was collected between 10 and 11 a.m., in order, as far as possible, to minimize these factors and to obtain comparable results, bearing the same relation to the digestive cycle.

Of the pathological factors, diabetes mellitus (8), arteriosclerosis (27), and

a moderate infection in a patient who is resisting well (30) are often associated with a rise in blood cholesterol, whereas in severe anaemias (13) and in many acute infections the cholesterol content of the blood is usually low (28, 29). Reference to these factors, if necessary, will be made in the appropriate place.

Of recent years there has been an increasing tendency to employ the term 'nephrosis'. The main objection to its use at present is that different schools employ the term in entirely different senses, so that misunderstandings are very apt to occur. The German school of pathologists led by Munk (31) consider that all renal disease with oedema, apart from heart failure, should be classed as nephrosis, whereas cases showing haematuria, uraemia, and cardio-vascular complications constitute nephritis. Thus either variety may occur as a pure type, or, perhaps more commonly, one variety may complicate the other in any given case. Many British pathologists, however, regard all renal diseases as toxaemic in origin, degeneration occurring first, and an inflammatory reaction making its appearance later, the degeneration being in itself an inflammatory process whether followed by reaction or not (32).

It has been decided, therefore, not to employ the term 'nephrosis' at all, but to indicate clearly in each case the presence or absence of oedema, which appears to be the important factor associated with changes in the blood cholesterol in nephritis.

In attempting to explain differences which have occurred in the results obtained by various observers, it is obvious that two main factors may be concerned. The first is concerned with the method of estimation employed. The older results may be open to doubt on this account, but, using the method of Wardell and Myers, as many of the recent workers have done, satisfactory results are obtained as long as full precautions are observed.

The second source of discrepancy lies in differences in classification, particularly in the chronic types of parenchymatous and interstitial nephritis. To remedy this possible fallacy, a description will be given, under each group, of the main clinical and pathological findings upon which the diagnosis is based.

Results of Observation on Clinical Cases.

Group I. Acute nephritis. Twenty-two cases. Under this heading are included all cases in which there was a sudden onset of the disease in a patient whose kidneys, as far as could be ascertained, were previously healthy. The clinical evidences of acute nephritis were: (1) oedema, which was a feature of twelve cases; (2) haematuria and the passage of red cell casts in the urine, which occurred in fourteen cases, in six of which no oedema was present at any time; and (3) albuminuria, which of course occurred in all cases apart from the presence of haematuria.

An attempt has been made to present an adequate summary of the relevant clinical features of these cases in Table I. In this table the cases are divided into three sub-groups. In the first sub-group are included those cases, eight in number,

in which oedema was present at the time of the first plasma cholesterol estimation; the relative severity of the disease is also indicated in this table. The four cases in the second sub-group were all comparatively slight, and in each case the oedema had disappeared less than ten days before the patient was admitted to hospital. With one exception (Case 110) all the patients in the above two groups were completely free from oedema before their discharge, and, as a rule, there was also not more than a trace of albumin in the urine at that time. The third sub-group consists of six cases in which no renal oedema had ever been present, the diagnosis being made on the history and the presence of blood and red cell casts in the urine.

Table I.

Acute Nephritis.

No.	Sex.	Age.	Intensity of Oedema.	Total Duration of Oedema.	Initial Plasma Cholesterol. Grm. %.	Remarks.
Group I. *Cases in which oedema was still present at the time of the first estimation.*						
5	M	21	Marked	7 months	0·31	For recovery stage see Table II
40	F	13	Slight	1 month	0·24	—
55	F	14	Marked	5 weeks	0·27	See Chart I
66	F	5½	Slight	2 weeks	0·24	See Chart II
72	M	4½	Very slight	Less than 2 weeks	0·22	See Chart III
110	F	18	Marked	3 months	0·36	—
180	M	32	Moderate	3 weeks	0·26	—
181	F	4	Marked	3 months	0·39	—
Group II. *Cases in which the oedema had disappeared shortly before the time of the first estimation.*						
128	F	16	Very slight	1 week	0·11	—
138	M	15	Slight	3 weeks	0·17	See Chart IV
145	M	15	Slight	2 weeks	0·11	—
157	F	14	Very slight	Less than 1 week	0·09	—
Group III. *Cases in which oedema had never been present.*						
48	F	23	—	—	0·15	For recovery stage see Table II
96	M	6	—	—	0·18	—
124	F	4½	—	—	0·14	—
164	F	4½	—	—	0·20	—
169	M	15	—	—	0·16	—
170	F	19	—	—	0·10	—

In addition to the above-mentioned eighteen cases, a further series of six cases was investigated, each of which had had acute nephritis many months or years before. On investigation, there were no symptoms of ill health, there was no cardio-vascular hypertrophy, the urine contained practically no red cells nor casts, and no abnormal number of white cells, and there was not more than a faint trace of albumin. It may therefore reasonably be claimed that these patients represent a 'healed' or inactive stage of nephritis, although this does not mean that their kidneys have returned to normal; they are liable to relapse, and indeed one case (No. 48) did so during the course of this investigation. Their

TABLE II.

The 'Healed' Stage of Nephritis.

No.	Sex.	Age.	Duration of Original Attack and Relapses.	Oedema in Original Attack.	Haematuria in Original Attack.	Date of Investigation.	Findings. Blood Urea.	Findings. Plasma Cholesterol.	Blood-pressure.	Urine.	Remarks.
							%.	%			
5	M	21	Jan.-Oct. 1925	Marked	Absent	March 25, 1926	0·020	0·16	130/75	No albumin No cells No casts	See also Table I for oedematous phase
48	F	22	Aug.-Oct. 1921 March 1922 March 1926	None	+ +	Aug. 10, 1925	0·023	0·13	135/64	Free of albumin A few red cells No casts	See also Table I
113	M	36	November 1923 February 1924	Slight	Microscopic	Jan. 28, 1926	0·030	0·14	115/65	Faint trace of albumin No cells No casts	—
130	M	13	Jan.-May 1924	Marked	+	March 30, 1926	0·025	0·19	110/65	Trace of albumin No cells No casts	—
135	M	30	2 weeks. Nov. 1923	Slight	Microscopic	March 5, 1926	0·034	0·15	116/70	Trace of albumin No cells No casts	—
160	F	34	July-Oct. 1920	Moderate	+ +	May 1, 1926	0·030	0·15	135/80	Trace of albumin No cells No casts	—

main features of interest and the clinical findings are set out in Table II, while two of these cases (5 and 48) are included in which the findings during the acute phase of the disease have already been given in Table I.

A study of Table I (Group I), dealing with the active phase of the disease, shows constant and definite deviations from the normal. In the first place, every case in which oedema was present at the time of the original investigation showed some degree of hypercholesteraemia, and, as is also indicated in the table, the increase of cholesterol in the blood plasma is roughly proportional to the degree of oedema present.

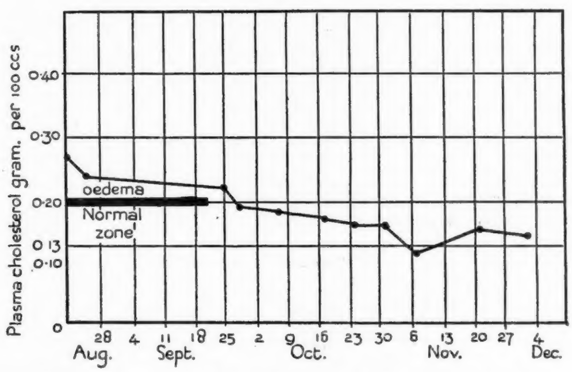

CHART I. Case No. 55. Acute nephritis, severe attack.

It might be argued that the initial figure of 0·22 per cent. in Case 72 was so nearly normal as to be within the limits of experimental error. That this is not so is suggested by the fact that within a fortnight the plasma cholesterol had fallen to 0·15 per cent. (Chart III), the form of the curve in this case being similar in shape to, although less pronounced than, those found in other comparable cases.

Five out of the eight cases were followed, at more or less frequent intervals, until they had reached a quiescent phase of the disease, and the curves obtained in three of these cases, one severe, one moderate, and one slight, are appended in Charts I–III. The other curves were similar in shape, so that consistent results were obtained in all cases.

It will be noticed from these charts that, even on the first estimation, the plasma cholesterol is already at its highest point, and that, as the oedema diminishes, so the cholesterol approaches normal figures. The only difference in the curves is one of degree, the fall occurring more quickly in the slighter cases, as might be expected, and in no case, however mild, did the plasma cholesterol fall to normal until, at least, several days had elapsed after the oedema had completely disappeared clinically.

One curious phenomenon was observed in six cases, the curves of which were followed. The cholesterol curve, having reached normal limits, proceeded to dip below the normal for a period of one or two weeks, and then returned within normal limits. The point is illustrated by reference to Charts I, II, and

IV, and may be only a coincidence, but a possible significance of this occurrence will be discussed later.

In four of the cases of this type set forth in Table I (Group II), the oedema had already disappeared before the first investigation was made; these were all comparatively mild cases. It will be seen that in each case the plasma cholesterol, at the time of the first estimation, was either normal or even subnormal, and reference to Chart IV shows that, even with an initial normal finding, the finding a week later was a low plasma cholesterol with a subsequent rise to normal. The curve in each of these cases showed a striking resemblance to the post-oedematous

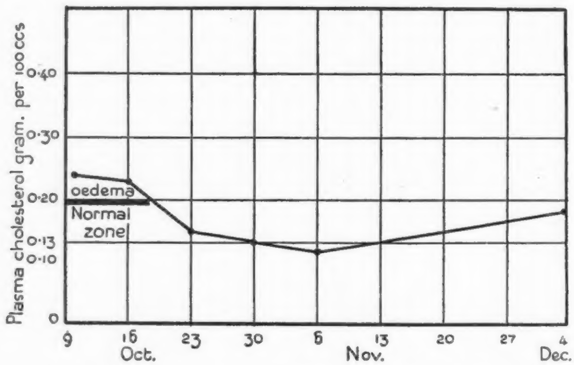

Chart II. Case No. 66. Acute nephritis, mild attack.

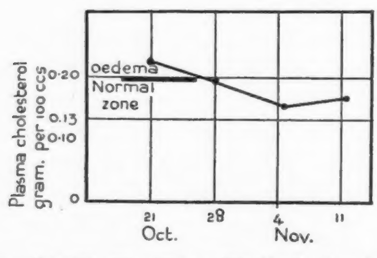

Chart III. Case No. 72. Very mild attack of acute nephritis.

phase of the cases which were oedematous on first examination, and it seems reasonable to assume that, if they had been investigated sufficiently early, the initial phase of cholesterol increase would have been observed in them also.

In the remaining six cases in Table I (Group III) there was no oedema at any time, and the diagnosis was made on the presence of blood and casts in the urine. In one case only was the plasma cholesterol slightly below the normal limit, and for no apparent reason. In the other cases the figures obtained were within the limits already accepted as normal.

For purposes of comparison, a further series of six cases is tabulated in Table III. All of these cases had haematuria without oedema, but in none of them was the condition due to nephritis. It will be seen that the figures in

this series also were within normal limits, with the exception of one case in which a reading of 0·12 per cent. was noted. Thus there is no difference in the plasma cholesterol between cases of haematuria of nephritic or of any other origin, and this investigation is of no value in attempting to distinguish between them.

TABLE III.

Haematuria not due to Nephritis.

No.	Sex.	Age.	Plasma Cholesterol. %.	Cause of Haematuria.
15	M	10	0·14	Oxaluria
62	M	15	0·20	Staphylococcal pyelitis
75	M	16	0·14	Postural, following long rest splinted in dorsal position
80	M	18	0·17	Bacillus coli pyelitis
133	F	29	0·12	Bacillus coli pyelitis
139	M	19	0·14	Accidental rupture of kidney

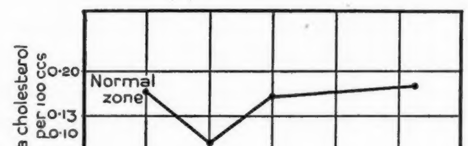

CHART IV. Case No. 138. Very mild attack of acute nephritis. The first estimation was performed a few days after oedema had disappeared.

The final series of observations on cases of acute nephritis was made on six cases in each of which the acute attack had occurred some considerable time previously. As has already been stated, such cases are considered to represent either a 'healed' or at least a quiescent stage of the disease, with presumably some degree of scarring and fibrosis in the kidney as the residual lesion. The results obtained from these six cases are set forth in Table II. The interval which had elapsed since the acute attack varied from six months to six years, and in each case the plasma cholesterol was within the normal limits. In Case 5 the finding in the acute stage is seen in Table I, and in Case 48, which belonged to the non-oedematous group, although the patient showed little or no evidence of renal disease at the time of the initial observation, a combination of acute tonsillitis and salpingitis was apparently responsible for a recrudescence of the haematuria seven months later. The result of a further investigation during this acute phase is seen in Table I; there was only a slight difference, almost within the limits of experimental error, between the findings on these two occasions.

Kahn (2) has stated that there is no alteration of the blood cholesterol in

acute nephritis. In his paper, however, he makes no mention of the clinical condition of his patients, so that it is not clear to which type of nephritis he refers. From a consideration of the present series of cases, it is seen that there is a slight but definite rise in the plasma cholesterol, which is always associated with oedema, and is indeed roughly proportioned thereto. As the disease progresses towards recovery, and this type usually does so, the oedema disappears, and this is followed after a short interval by a return of the plasma cholesterol to within, and even perhaps below, the normal limits. Albuminuria disappears last of all, and exhibits no apparent relation to the plasma cholesterol. As is shown also by the charts, a slightly raised or rapidly falling plasma cholesterol occurs in the milder cases, and is thus of relatively good prognostic significance, whereas a high or slowly falling curve indicates that the disease will run a prolonged course, and perhaps foretells a subacute or chronic parenchymatous nephritis.

Group II. *Chronic parenchymatous nephritis and chronic nephritis. Thirty cases.* In this group the majority of the cases had albuminuria of relatively marked degree, as a rule coupled with varying amounts of clinical oedema, although in four cases (Nos. 20, 98, 115, and 162) oedema was never known to have been present. In addition, one or more of the following features were also usually present: (1) haematuria, or at least the presence of red cells in the centrifugalized deposit, and various types of cast in the urine; (2) urea retention; (3) cardio-vascular changes; (4) anaemia, with a peculiar pale and sallow complexion; and (5) the presence of the typical retinal changes.

To the group exhibiting oedema and little permanent cardio-vascular change, the term chronic parenchymatous nephritis is applied, whereas those cases in which the oedema was absent and the cardio-vascular changes were marked are classified as chronic nephritis. The four cases mentioned above, which had never been known to exhibit oedema at any time, were included in this group chiefly on account of their sallow complexion and anaemia, the relatively large quantity of albumin in their urine, the tendency to raised blood-pressure and urea retention, and the typical exudative changes in the retina. Their differentiation from chronic interstitial nephritis will be more fully discussed in the section devoted to the latter condition.

The cases included in the present group are detailed in Tables IV and IVa. In the former will be found all cases of chronic parenchymatous nephritis in which there was no vitiating factor; in the latter are placed seven cases in which clinical uraemia was present on the first investigation. As much clinical detail as possible has been compressed into the table; the figures quoted for the blood-pressures were those taken on the most recent occasion previous to the cholesterol estimation.

A consideration of the results obtained in this group of cases reveals the following facts. In altogether fourteen of the cases renal oedema was clinically present at the time of the first investigation, and, with only one exception (Case 82), there was a definite increase in the plasma cholesterol in these cases. These results agree with those of the majority of authors quoted above.

TABLE IV.

Chronic Parenchymatous Nephritis and Chronic Nephritis.

Findings on First Investigation.

No.	Sex.	Age.	History of Oedema.	Urinary Findings.	Blood-pressure.	Oedema.	Blood Urea %.	Plasma Cholesterol %.	Remarks.
2	M	19	Slight oedema 6 months previously. Lasted about 3 months	Deposit: a few R.B.C. and hyaline casts. Haematuria at onset.	140/98	Absent	0·05	0·15	—
12	M	10	Fluctuating oedema for 14 months	Deposit: no R.B.C. A few hyaline and granular casts	120/85	Slight	0·04	0·37	—
13	M	34	Fluctuating oedema for 18 months	Deposit: no R.B.C. Occasional granular casts	125/70	Slight	0·04	0·34	—
24	M	49	Renal oedema 9 months previously. Lasted 4 months	Deposit: no R.B.C. nor casts	225/125	Slight oedema of cardiac type	0·06	0·17	A 'mixed' type of nephritis, in which the cardio-vascular changes predominated
27	M	40	Oedema 6 months previously. Lasted 1 month	Deposit: a few granular and hyaline casts. No cells	135/100	Absent	0·14	0·10	—
35	F	41	Intermittent oedema for 6 years	Deposit: a few R.B.C. Many hyaline and granular casts	230/140	Absent	0·05	0·23	—
37	F	19	Constant oedema for 6 months	Deposit: a few R.B.C. and hyaline casts	215/135	Moderate	0·07	0·73	See Chart V
60	F	42	Generalized oedema 10 years previously. Lasted about 4 months	Deposit: very few R.B.C. Many granular casts. Occasional frank haematuria	230/120	Absent	0·07	0·22	See Chart VII

TABLE IV (*continued*).

No.	Sex.	Age.	History of Oedema.	Urinary Findings.	Blood-pressure.	Oedema.	Blood Urea %.	Plasma Cholesterol %.	Remarks.
79	M	13	Fluctuating oedema for several months, although intermittent for 8 years	Deposit: very few R.B.C. and granular casts	110/70	Marked	0·03	0·33	Also had amyloid disease of the kidney. See text and Chart VI
84	M	54	Swelling of legs 2 months	Deposit: a few R.B.C. Many hyaline and granular casts.	150/80	Marked	0·04	0·48	—
85	M	54	Fluctuating oedema of moderate severity for $3\frac{1}{2}$ years	Occasional bursts of haematuria. Deposit: many hyaline and a few granular casts	160/90	Slight	0·03	0·44	—
86	F	33	'Kidney trouble' 13 years before. Clinical oedema 1 month only	Deposit: many R.B.C., granular and hyaline casts	130/80	Slight	0·04	0·029	—
98	M	49	Never known to have oedema	Deposit: a few R.B.C. A few granular casts	260/150	Absent	0·08	0·027	See text
101	M	11	Moderate oedema for 6 months	Deposit: no cells; no casts	100/80	Slight	0·02	0·27	—
107	M	28	Recurrent attacks of oedema for 8 years	Occasional haematuria. Deposit: many R.B.C. and granular casts	165/130	Slight	0·03	0·26	—
121	F	34	Occasional puffiness only during previous year	Deposit: many R.B.C. and hyaline casts. A few granular casts	220/165	Absent	0·04	0·14	—

134	M	37	Slight oedema for 1 year	Deposit: no cells; no casts	110/65	Slight	0·03	0·24	—
140	F	30	Recurrent attacks of oedema for 20 years	Deposit: many R.B.C. A few granular casts	220/140	Absent	0·05	0·25	—
149	F	46	Slight oedema Jan. 1916 until Jan. 1920 at intervals	Deposit: a few R.B.C. and granular casts	210/135	Absent	0·04	0·175	—
165	M	52	Oedema of 2 months' duration localized to legs	Deposit: a few R.B.C.; many granular, hyaline, and fatty casts	235/135	Marked. Confined to legs	0·06	0·44	Comparable with Case 84. See text
167	M	37	Indefinite puffiness for 3 years	Deposit: many R B.C. A few hyaline and epithelial casts	125/70	Absent	0·09	0·07	—
172	F	43	Oedema 4 years previously. Duration 2 months	Deposit: no cells; no casts. (No albumin present.)	210/100	Absent	0·04	0·18	Included in this group on account of high blood-pressure
177	F	44	Intermittent oedema for 5 years	Deposit: no R.B.C. Many granular and hyaline casts	140/95	Slight	0·03	0·48	—
179	F	9	Oedema 6 weeks, but persistent	Deposit: a few R.B.C. and granular casts	115/85	Marked	0·09	0·30	Oedema did not disappear during life

TABLE IVa.

Chronic Nephritis with Uraemia.

Findings on First Investigation.

No.	Sex.	Age.	Oedema.	Blood Urea %.	Plasma Cholesterol %.	Blood-pressure.	Remarks.
20	M	25	Absent	0·275	0·17	160/100	Had never been oedematous
78	F	20	Absent	0·41	0·15	265/165	Indefinite history of puffiness for several months
82	M	45	Moderate. Chiefly of legs	0·17	0·20	120/70	Had had renal oedema for several months. See clinical note
102	F	33	Absent	0·18	0·31	116/68	Slight oedema 3 months previously
115	M	39	Absent	0·40	0·15	105/90	Had never been oedematous
162	M	31	Absent	0·16	0·18	195/130	Had never been oedematous

TABLE V.

Uraemia.

No.	Blood Urea. %.	Plasma Cholesterol. %.	Diagnosis.	Remarks.
79	0·26	0·40	C. P. N.	See Table IV and Chart VI
102	0·26	0·24	C. P. N.	See Table IV
20	0·275	0·17	C. N.	—
60	0·54	0·15	C. N.	See Table IV
78	0·41	0·15	C. N.	—
82	0·21	0·13	C. N.	See Table IV
115	0·40	0·15	C. N.	—
140	0·16	0·18	C. N.	See Table IV
162	0·16	0·18	C. N.	—
29	0·29	0·12	C. I. N.	—
53	0·67	0·15	C. I. N.	—
58	0·24	0·18	C. I. N.	—
99	0·40	0·13	C. I. N.	—
127	0·40	0·16	C. I. N.	—
143	0·29	0·17	C. I. N.	—
173	0·26	0·14	C. I. N.	—
43	0·275	0·09	Acute retention of urine	Pyelonephritis
59	0·34	0·14	Acute retention of urine	Carcinoma of bladder
69	0·17	0·06	Chronic retention of urine	Pyaemia following prostatectomy
77	0·08 rising	0·07	Calculous anuria	—
97	0·30	0·09	Acute retention of urine	Urethral stricture. Suprapubic cystostomy
154	0·69	0·19	Acute retention of urine	—
155	0·21	0·13	Chronic retention of urine	—
156	0·275	0·09	Obstructive suppression of urine	Carcinoma of cervix

C. N. = Chronic nephritis.
C. P. N. = Chronic parenchymatous nephritis.
C. I. N. = Chronic interstitial nephritis.

Henes (9) goes so far as to doubt whether renal oedema ever occurs without some increase in the plasma cholesterol. The only possible exception to this generalization in the present series of cases occurred as follows:

Case 82. Male, aged 45. While under treatment for myasthenia gravis he was found to have nephritis, as was evidenced by marked puffiness, albuminuria (0·1 to 0·4 per cent.), and the presence of blood and occasional casts in the urine. Blood-pressure 135/95. About the same time the myasthenia disappeared.

He also had a severe secondary anaemia (R.B.C. 2,160,000 per cu. mm., Hb. 39 per cent.) and regular evening pyrexia (99°–101° F.).

The blood analyses were as follows:

Nov. 6, 1925,	blood urea	0·17 per cent.,	plasma cholesterol	0·20 per cent.
Nov. 13, 1925,	„ „	0·135 „ „	„ „	0·15 „ „
Jan. 7, 1926,	„ „	0·21 „ „	„ „	0·13 „ „

During December and January the patient developed marked oedema of the legs without, at first, other evidence of heart failure, but it is probable that, in the later stages at least, this latter factor played a large part in the production of the oedema.

Death occurred on January 27, 1926, and the following lesions were found at post-mortem: (*a*) recent ulcerative endocarditis of the aortic valve cusps; (*b*) large white kidneys.

Microscopical report: 'Sections show general vascular engorgement with varying degrees of fatty degeneration of the tubular epithelium. Some proliferation of the subcapsular epithelium and patchy cell infiltration suggesting early contraction. There is no microscopical evidence of embolic focal nephritis.'

Clinically, the assumption seems justified that in November, at least, the slight degree of generalized oedema in this patient was renal in origin. If this be correct, then this case forms an exception to the general rule. The reason for the absence of cholesterol retention can be explained in the following way. On the one hand, there was renal oedema, which would ordinarily be accompanied by a rise in the plasma cholesterol, but, on the other hand, this was more than counterbalanced by the opposing factors, profound anaemia, uraemia, and severe infection possibly of the blood-stream, originating from the aortic valves.

It is thus accepted that in the vast majority, at least, of cases showing renal oedema there is cholesterol increase, just as occurs in acute nephritis with oedema. But, on the other hand, there are certain differences, both in the degree and in the form of the curve, when the two conditions are compared.

The initial value is, on the whole, considerably higher in this type than in the acute stage, and it will also be noted that the amount of oedema present is no guide to the amount of cholesterol present in the plasma; thus Case 37, with only moderate oedema, gave a cholesterol figure of 0·73 grm. per cent., whereas in Case 79, where there was an extreme degree of oedema, the corresponding figure was only 0·33 per cent.

Again, the majority of these cases were followed at intervals for a con-

siderable time. In some cases, the oedema practically disappeared within a short space of time, leaving the patient with a considerable quantity of albumin in the urine, and perhaps an increased blood-pressure with cardio-vascular changes. A typical example of this condition is seen in Chart V (Case 37). The patient was a girl aged 19 who had exhibited a slight degree of generalized oedema in February 1925. This almost disappeared in April, although she still remained puffy, but in June the oedema became more marked again, to an even greater degree than it had previously attained. At the end of June, when exhibiting a

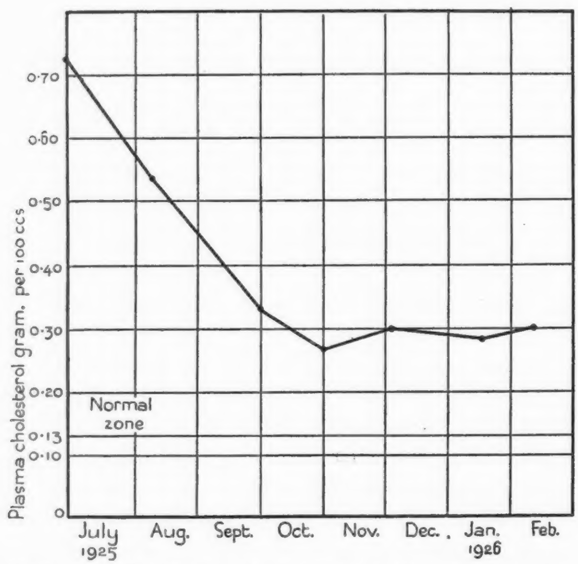

CHART V. Case No. 37. Chronic parenchymatous nephritis with cardio-vascular changes.

moderate degree of oedema, the plasma cholesterol was 0·73 per cent., the blood urea 0·07, and the blood-pressure 215/135. The oedema had disappeared clinically about the beginning of September, and it will be seen that during this period there was a marked fall in the plasma cholesterol. In the non-oedematous stage the cholesterol reached a fairly constant level in the region of 0·3 per cent. and remained stationary about that figure.

Thus, in this type of case, the plasma cholesterol in the oedematous phase is much higher than it is in acute nephritis, and in the non-oedematous phase there is a tendency, amongst the more recently oedematous cases, for the cholesterol to fail to reach the normal limits.

In another group of cases oedema, usually slight in degree, persisted throughout the period of observation. Examples of this type occurred in Cases 13, 84, 85, 165, and 179.

While not exhibiting the figures from these cases in the form of charts, as there is little to be gained by doing so, the results in one of the cases are quoted:

Case 13.	June 5, 1925,	plasma cholesterol	0·34 per cent.		
	Oct. 29,	„ „	„	0·40 „ „	
	Nov. 5,	„ „	„	0·39 „ „	
	Nov. 11,	„ „	„	0·36 „ „	
	March 20, 1926,	„	„	0·32 „ „	

During the whole of this period the patient exhibited a slight degree of oedema only.

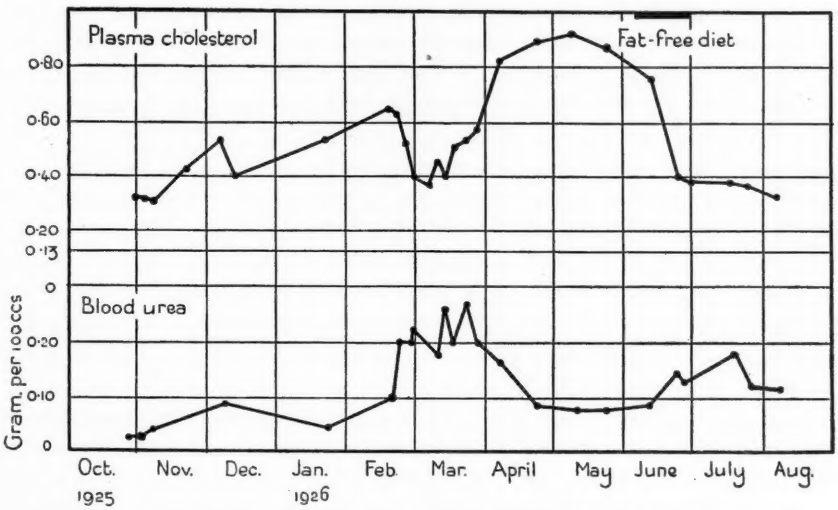

Chart VI. Case No. 79. Chronic parenchymatous nephritis. This case is described in the text.

In a third, and rarer, group of cases, of which only one (Case 79) was followed through for any length of time, the oedema waxed and waned, sometimes being tremendous, at other times absent. The curve is recorded in Chart VI.

The patient was a boy aged 13 who had had an aural discharge for eight years. Oedema followed a mastoid operation in 1917 and was noted at intervals, but became very marked a few months before admission, on October 29, 1925. At that time he was completely waterlogged, the face being especially affected. The urine contained much albumin ; blood-pressure 112/72. The oedema rapidly subsided following a salt-free diet and mastoid drainage, but the patient developed a uraemic condition with a very low alkali reserve and other evidence of an acidosis.

On relaxing the diet the patient lost his symptoms of uraemia, but the oedema rapidly returned, and thereafter fluctuated irregularly until the time of his death from a pneumococcal septicaemia in November 1926. At the post-mortem examination the kidneys were found to be small and of a yellowish-grey colour. The capsules showed fine adhesion to the renal cortex. The tubules were

markedly degenerated, with deposits of doubly refracting fat. There was also some small round-celled infiltration between the tubules and evidence of commencing fibrosis.

In addition to the above changes, there was an extensive amyloid deposit throughout the renal parenchyma; the other organs showed relatively little amyloid change. A more detailed account of the features of this case has already been published elsewhere (33).

A study of the curve in this boy shows that the degree of oedema has little or no relation to the actual quantity of cholesterol in the blood plasma. From October 1925 to May 1926 the tendency was for the plasma cholesterol to rise, until the maximum figure of 0·92 per cent. was reached. The upward curve was broken by the uraemic interlude in February 1926, being markedly depressed at that time. It is noteworthy, however, that, on the termination of this disturbing factor, the cholesterol curve resumed its upward trend, and appears in the chart almost as a straight line broken by the downward reaction to the uraemic acidosis. In effect it will also be noticed that, in the uraemic portion of the curve, the lines denoting cholesterol and urea are complementary.

Another point of interest in this case was the rapid decline which occurred in the plasma cholesterol a few days after placing the patient on a fat-free diet. At the same time, however, there was no appreciable change in his general condition.

An investigation carried out on the day before his death from pneumococcal septicaemia showed that the plasma cholesterol had risen again to 0·60 per cent., there being marked pitting of the legs and slight oedema of the face on this occasion. Taking into consideration the fact that the patient was succumbing to an acute infection, the final figure must be regarded as unexpectedly high.

This case tends to show, however, that there is no definite relation between oedema and the cholesterol content of the plasma. It suggests rather that they are concomitants, possibly due to the same underlying pathological change, rather than that they bear the relation of cause and effect one to the other.

Four cases showed localized oedema only and will be discussed later. Of these, Nos. 79 and 82 have been already described, leaving Cases 84 and 165 for a brief description here. Both were males of middle age who exhibited oedema sharply localized to the legs and lower abdomen, marked albuminuria with a few white cells and granular casts in the urine, as well as a diminished chloride output. The blood-pressure was normal in Case 84 and raised in Case 165. Blood examination showed cholesterol values between 0·4 and 0·6 per cent. in each case. At autopsy the only lesions found were cloudy swelling of the tubules without fatty degeneration, and a slight swelling and cellularity of the glomeruli. On the whole there was singularly little change in the kidneys, but nothing at all demonstrable in the other organs to account for the clinical picture which was suggestive of chronic parenchymatous nephritis.

Of the sixteen cases which did not show any oedema at the time of the first investigation, nine yielded plasma cholesterol values which were either within

normal limits or even subnormal (e. g. Cases 27 and 167). In four cases, however, Nos. 35, 60, 102, and 140, there was some degree of hypercholesterinaemia, varying from 0·22 to 0·31 per cent. in patients whose oedema had subsided months or even years before. In one other case also (No. 98) a figure of 0·27 per cent. was found, although the patient was never known to have had oedema, and was included in this group only on the general clinical grounds detailed in the section dealing with this condition.

The point which emerges from a study of these latter five cases is that a persistent increase in the plasma cholesterol several months or longer after the disappearance of oedema is a bad sign. Of these cases Nos. 60, 102, and 140 died either during the period of observation or shortly thereafter in acute uraemia, No. 35 is in a state of 'chronic' uraemia, with a blood urea in the region of 0·15 per cent., while No. 98 is stationary, although he has marked cardio-vascular damage and a blood urea constant about 0·07 per cent.

The effect of uraemia upon the cholesterol findings is seen most clearly in Table IVa. Here are tabulated the details of six cases of this type of nephritis in all of which uraemia was present at the time of the first investigation. For the diagnosis of uraemia the usual clinical phenomena were employed, with the addition of a raised and rising blood urea, although no actual figure is accepted below which it is held that uraemia cannot be present. Normal cholesterol figures were found in five cases, in one of which (No. 82) renal oedema was probably present; this case has already been discussed. In the remaining case (No. 102) a high figure was found (0·31 per cent.), although, as the condition progressed, the cholesterol decreased to 0·24 per cent. three weeks before the patient's death. For comparison with these cases, a complete series of cases of uraemia from all varieties of causes is appended in Table V. In this are included nine cases which have already appeared in either Table IV or IVa, but in most of these cases the final figure is quoted in contrast to the initial figures recorded in the earlier tables. Cases 20, 78, 115, and 162, however, were only investigated on one occasion, so that their findings given in both tables refer to the same date.

In all cases in which uraemia occurred in the course of chronic interstitial nephritis and in the mechanical group, the figures were normal or low, as also were they in the terminal stages of seven out of the nine cases of chronic parenchymatous and chronic nephritis. Of the remaining two cases, No. 79 has already been described and his curve discussed (Chart VI), while in Case 102 the plasma cholesterol fell from 0·31 to 0·24 per cent. within five weeks, and the blood urea rose from 0·17 to 0·26 within the same period.

It is thus seen that, as a general rule, to which, however, there may be exceptions, the plasma cholesterol tends to fall as uraemia supervenes, while no definite relationship is usually seen between the relative amounts of these two substances in the blood-stream. The course of Case 60 is illustrated in Chart VII, where the gradual fall in cholesterol is seen; the other cases observed followed a similar course, with the exception of Case 79 (Chart VI), which has already been

discussed, and shown to be exceptional in that the blood urea fell with a corresponding temporary improvement in the patient's condition.

On the whole, therefore, these results agree with those of Henes (9), who claims a normal or low blood cholesterol to be the general rule in cases of uraemia, although the exceptional cases in this series showed higher figures than were recorded by him.

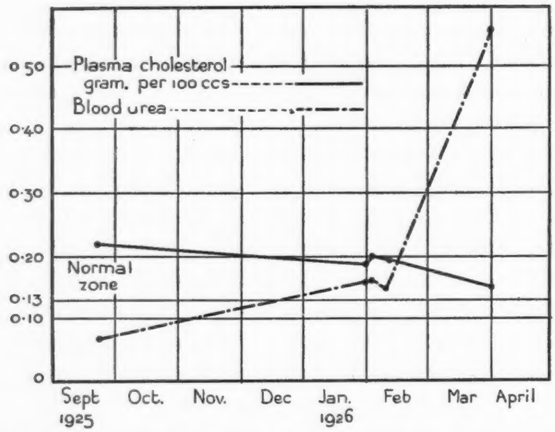

CHART VII. Case 60. Chronic nephritis with onset of uraemia.

Two additional series of control cases, showing other types of oedema, were investigated. In the first, ten cases of oedema due to heart failure were selected, and all gave normal values, with the exception of one case (No. 93) in which a value of 0·27 per cent. was found. This patient was suffering from advanced arteriosclerosis (q. v.) with auricular fibrillation, and the rise in plasma cholesterol must be explained by the presence of the arterial disease.

The other series consisted of sixteen cases of pregnancy toxaemia. It has already been stated that pregnancy is associated with a rise in the plasma cholesterol (4, 21). It would therefore be expected that, if the pathological processes were similar in parenchymatous nephritis and in toxaemia of pregnancy associated with oedema, very high figures would have been recorded in the latter condition from a combination of the two factors. The results of this series will be found in Table VI, and it will be seen that consistent results were not obtained, an unexpected number of cases yielding normal or even low figures. It might be thought that the severity of the condition could be gauged by the mortality, but in this series all the cases recovered. There is no convenient method of estimating the relative degree of toxaemia in this condition other than that of clinical observation. Applying this method to the present series of cases, on the whole it was found that those patients who were most severely toxic were those in whom the lowest values were found.

The explanation which suggests itself is that this condition is similar to uraemia, in that a toxin exercises a markedly depressant effect upon the plasma

cholesterol; thus several of the cases in this series may possibly furnish examples of a condition of oedema similar in origin to renal oedema, in which normal cholesterol figures were found.

TABLE VI.

Toxaemias of Pregnancy.

No.	Duration of Pregnancy in Months.	Blood Urea %.	Plasma Cholesterol %.	Oedema.	Remarks.
14	8½	0·04	0·12	+	Developed eclampsia. Recovered
49	8½	0·02	0·12	0	Albuminuria only. Recovered
65	8½	0·03	0·19	+ + +	Eclampsia. C.S. Recovered
76	8½	0·02	0·20	+ +	Eclampsia. Recovered
109	7½	0·025	0·18	+ +	Twins. Eclampsia. Recovered
112	8½	0·03	0·15	+	Toxaemia only. Recovered
117	9	0·02	0·21	0	Mild toxaemia. Recovered
129	9	0·035	0·22	+	Toxaemia. Recovered
136	9	0·04	0·38	+ + +	Eclampsia. Recovered
141	8½	0·03	0·20	+ +	Triplets. Post-partum eclampsia. Recovered
142	9	0·02	0·32	+	Mild toxaemia. Recovered
143	8	0·025	0·44	+	Mild toxaemia. Recovered
151	8½	0·055	0·21	+	Mild toxaemia. Recovered
152	9	0·03	0·17	0	Albuminuria. Recovered
153	8½	0·03	0·26	0	Albuminuria. Recovered
178	9	0·03	0·20	+ +	Toxaemia. Recovered

Group 3. Chronic interstitial nephritis, arteriosclerosis, and hyperpiesia. 34 cases. None of these cases had ever been known to suffer from oedema of a renal type, but a few had previously had heart failure with oedema of the legs. Cardiac oedema was, however, only present in one case (No. 93) at the time that blood was taken for cholesterol estimation. The clinical differentiation of the various chronic forms of vasculo-renal disease is often a matter of considerable difficulty. In all of the cases considered, the diagnosis had perforce to be made entirely on clinical grounds, although in some few cases pathological confirmation at autopsy was available.

The arteriosclerotic cases were easily distinguishable. All showed calcification of the tunica media of their medium-sized arteries and were thus identified by palpation and by X-rays of their limbs.

The hyperpietic cases belonged to a less readily recognizable group. All showed persistent hypertension with cardio-vascular symptoms. Thus patients of this group complained of headaches, giddiness, dyspnoea on exertion, or oedema of the lower extremities. On examination, they were usually of good physique, florid in complexion, and well nourished. On examination, the left ventricle was hypertrophied and the blood-pressure raised; the aortic second sound was accentuated. The urine was clear and of a good colour and specific gravity, with no albumin or only a trace, and occasional hyaline and granular casts, and there was no evidence of renal disease other than the trace of albumin sometimes present in the urine with occasional casts. The whole clinical aspect of these cases is cardio-vascular.

In chronic interstitial nephritis the patients showed evidence of renal disease.

They tended to be pale and had often lost weight. On examination, the urine contained more albumin, often blood-cells, and more casts than were found in the preceding group. Retinal examination frequently showed circumscribed points and patches of exudate in addition to the haemorrhages found also in the hyperpietic cases.

The distinction of chronic nephritis by a history of preceding renal oedema was comparatively simple, but four cases were never known to have been oedematous at any stage of their history (Nos. 20, 98, 115, 162). Their findings have already been discussed in the appropriate section, but as their diagnosis is intimately concerned with that of chronic interstitial nephritis, it has been thought advisable to consider it at this stage. In the first place, one could sometimes obtain a history of symptoms suggestive of a preceding nephritis, or of scarlet fever, or of some other infection commonly complicated by nephritis. In addition to this, the ages of the majority of the patients were considerably less than the age at which chronic interstitial nephritis is common. The patients themselves were more definitely pale and toxic, with marked wasting. The urine was pale and of fixed low specific gravity, with larger quantities of albumin, cells, and casts; there was in each case definite failure of the excretory function of the kidney. In addition to the retinal changes described above, 'cotton-wool' patches were found in this type of the disease. The pathological distinctions between these similar but separate conditions have been discussed by G. Evans (34), under whose care the great majority of the patients in the chronic nephritic and hyperpietic groups have remained for some time, and I am indebted to him for the clinical observations upon which many of the diagnoses are based.

(*a*) *Chronic interstitial nephritis.* Of this condition, fourteen cases were examined, and the results in all cases were within normal limits. The highest figure obtained was 0·19 per cent., and the lowest was 0·13 per cent., with an average reading of 0·16 per cent.

(*b*) *Hyperpiesia.* Fifteen cases examined yielded rather higher results than the cases in the preceding group. The highest recorded figure was 0·25 per cent. and the lowest was 0·09 per cent., with an average of 0·18 per cent. Of the fifteen cases, no fewer than seven showed cholesterol values of 0·20 per cent. or over, although in two cases subnormal readings were found for no apparent reason.

(*c*) *Primary arteriosclerosis.* The five cases in this group all showed a primary calcareous degeneration of the tunica media (Monckeberg's sclerosis). The highest value found was 0·40 per cent. and the lowest was 0·16 per cent., with an average of 0·29 per cent.

Thus it is seen that in chronic interstitial nephritis normal cholesterol values are the rule, whereas in primary arteriosclerosis they are the exception. The hyperpietic cases occupy a position midway between the two preceding groups, and the fact that the plasma cholesterol in many of these cases tends to have a higher value than is found in chronic interstitial nephritis would suggest that pathologically such cases are more nearly related to the arteriosclerotic group.

The last investigation to which reference will be made was the cholesterol content of oedema fluid. The results obtained were as follows:

Case.	Diagnosis.	Nature of Fluid.	Cholesterol Content %.	Plasma Cholesterol %.
82	Chronic nephritis	Oedema fluid (during life)	About 0·01	0·13
84	Chronic nephritis	(a) Oedema fluid. (b) Ascitic fluid. (Both obtained P.M.)	Very slight trace. About 0·01	0·05 (during life)
—	Morbus cordis. Mitral stenosis	Ascitic fluid (during life)	Very slight trace	—

Although very few specimens were examined, these results show that the increased plasma cholesterol is not accompanied by a high cholesterol value in the tissue fluids, and also that there is no appreciable difference between oedema fluid of renal or of cardiac origin, as far as their cholesterol content is concerned.

Discussion.

It may be accepted as a general rule that true renal oedema is accompanied by an increase in the cholesterol content of the plasma. The problem which arises is that of the relationship which exists between these two phenomena.

In the first place there are several conditions, both physiological and pathological, some of which have been mentioned above, in which the plasma cholesterol may rise to a very high level without the development of oedema. Therefore it can be stated quite definitely that renal oedema is not secondary to increase in the plasma cholesterol. On the other hand, it is not at all clear that the underlying cause of the oedema is also the cause of the cholesterol retention. Although renal oedema is usually associated with an increased cholesterol content of the blood plasma, yet one case (No. 82) appears to furnish a possible exception, and, as has also been pointed out, in the cases showing chronic oedema, the amount of cholesterol in the plasma bore no definite relation to the degree of oedema.

In addition to this, in the few cases in which oedema showed marked fluctuations over a period of months, the variations in the cholesterol curves were entirely independent of changes in the degree of oedema, and, in fact, were much more susceptible to the influence of such factors as infections, uraemia, and even apparently of a fat-free diet. This point is illustrated by reference to Chart VI.

In addition to this, if it be accepted that the oedema which occurs in the toxaemias of pregnancy is of the same nature as the oedema of nephritis, then we are furnished with a convincing series of cases in which the plasma cholesterol was normal in the face of the combination of pregnancy and oedema, which would have been expected, in combination, to raise the cholesterol to a very considerable height above the normal.

It seems probable, therefore, that while renal oedema and cholesterol retention

usually occur together, they are probably both dependent upon some underlying lesion which is the pathological basis of the disease, rather than that either bears the relation of cause or of effect to the other. The problem of the nature of the relationship between cholesterol retention and renal oedema will not be solved until we know more about the normal metabolism of cholesterol in the body, its synthesis and break-down products, and also about the extrarenal changes which occur in nephritis. The kidney does not excrete cholesterol in appreciable amounts and, as far as we know, does not synthesize it. Why, then, this increase in the amount of cholesterol being conveyed by the blood-stream?

Fischer (35) sums up as follows: 'The oedema observed in nephritis is not secondary to the loss of kidney function. Kidney disease does not lead to the development of oedema.' He concludes that 'it represents in the involved tissues the same type of change as that which in the kidney we call nephritis. The swelling of the kidney represents the same process as the swelling of the tissues of the body generally, and both of them are induced by the same cause.' Following this, we must consider the view of Epstein (36) that the condition is due to a metabolic disorder similar to that associated with hypothyroidism. Although not generally accepted, this view finds confirmation in the work of Du Bois and Aub (37), who found the basal metabolic rate diminished in nephritis with oedema. This investigation was only carried out in Cases 79 and 84 in the present series, and in each case was −20 per cent.

From a study of the fat metabolism in nephritis, Linder, Lundsgaard, and van Slyke (38) concluded that the oxidation of fat is carried out as readily as in health, but that the mechanism which transfers fat from the blood to the tissues is upset. It is also significant that Fahr (39) now apparently regards it as unlikely that simple tubular degeneration can cause renal oedema, and he has recently suggested that the process underlying the production of this type of oedema is not damage to the kidney tissue at all, but a change in the capillaries of the *Unterhautzellgewebe.*

It would seem, therefore, that more attention should be directed to the changes occurring in the body as a whole in nephritis, instead of confining ourselves almost exclusively to the kidneys. It is probable that there is some metabolic disturbance which affects especially the mechanism which transfers fat to the tissues, although it is not by any means certain, or even probable, that the main seat of the trouble is in the thyroid gland. It seems, in fact, much more likely that the same toxin which affects the renal tubules damages also all the cells of the body in some degree. It is unfortunate that tests of the function of the liver and suprarenal bodies are not yet sufficiently reliable to be applied in these cases, as it is conceivable, in view of the close connexion between these organs and cholesterol metabolism, that some alteration in function would be disclosed.

The idea of a toxin affecting the cells of the body tissues in general is supported to some extent by the occurrence of intense localized oedema in exceptional cases.

In Cases 84 and 165 the oedema was confined so strictly to the legs and lower part of the abdomen as to engender the suspicion of a mechanical venous obstruction, although this could not be demonstrated *post mortem*. In these cases, as has already been stated, the renal parenchyma was relatively little affected. In Case 79 the oedema was, at one time, almost entirely localized to the face, which was enormously swollen.

The occurrence of this atypical form of oedema in cases all of which were shown by autopsy to present solely the lesions of chronic parenchymatous nephritis (although in two cases the evidence of renal damage was slight, even under the microscope) does not seem capable of any explanation other than that the tissue cells of the particular areas affected were singled out for attack by some unknown toxin, while the renal parenchyma escaped relatively unscathed. The findings in these cases appear to lend support to the views of Fischer and of Fahr quoted above.

At the same time, in all of these cases, no matter how localized the oedema, and how little the apparent damage to the kidney, the high plasma cholesterol supports the view that the essential metabolic disturbance is very similar to that which occurs in the more typical cases of chronic parenchymatous nephritis. The plasma cholesterol, therefore, can be used diagnostically to furnish useful evidence as to the nature of a case showing oedema of doubtful origin.

A rather obscure point arises in connexion with the recovery stage of cases with acute nephritic oedema, and is best illustrated by reference to Chart II. After the initial rise there occurs a drop in the plasma cholesterol, which not only reaches the normal limits, but transcends them so that a subnormal figure is found for a space of a few days. This fall below the lowest normal limit was found to occur in six cases out of seven in which it was looked for, and the seventh was the very mild case illustrated in Chart III.

It is suggested that, as the acute stage of the disease is characterized by difficulty in the transference of fat to the tissues and a low basal metabolic rate, so the recovery stage is characterized by a temporary increase in the metabolism of cholesterol, so that the demand is, for a short time, in excess of the supply. As soon as the metabolic processes regain their accustomed equilibrium however, the cholesterol returns to within normal limits.

It has also been shown in this series that the cholesterol increase is confined to the circulating blood-plasma, and does not affect the tissue fluids, as is shown by the low figures found in oedema fluid. To this extent, it is correct to speak of a retention of cholesterol within the blood-stream. The next point which arises is the possible effect of a prolonged increase in the plasma cholesterol on the body tissues.

It has been stated by Russian workers, quoted by McNee (40), that changes in the intima of the larger arteries can be induced in rabbits by feeding them for a long time on a diet rich in cholesterol. On the other hand, herbivorous animals are not accustomed to cholesterol in the diet, and similar changes do not occur in carnivora when fed on a similar diet. At the same time, it is curious

that two of the diseases associated with prolonged hypercholesterinaemia, chronic nephritis and diabetes mellitus, are frequently associated with arterial lesions. The problem in diabetes has been studied by Labbé and his co-worker (41) in the arterial lesions of diabetic patients, and they conclude that hypercholesterinaemia, by encouraging the deposition of cholesterin in the region of previously produced chronic inflammatory lesions, chiefly situated in the intima, aggravates the hyperplastic tendency of vessels already diseased.

From the prognostic point of view it has been shown, in this present series, that those cases in which the plasma cholesterol is found to be above the normal limit long after oedema has disappeared are precisely the cases in which uraemia tends to supervene; they are, in fact, the cases in which the prolonged irritation has produced the most marked changes in the blood-vessels and in the renal parenchyma.

Conclusions.

1. Renal oedema is almost invariably associated with an increase in the plasma cholesterol. This increase may not be great, but even the slighter degrees are shown to be of definite significance, because, on following these cases, the cholesterol figures fall as the oedema disappears. This phenomenon is seen most clearly in cases of acute nephritis.

2. In acute nephritis with oedema, the plasma cholesterol is raised in degree proportionate to the amount of oedema. During the recovery stage the oedema first clears up, the plasma cholesterol next returns to normal and then usually becomes subnormal for a short time, and lastly the albumin practically disappears from the urine.

In a case of apparent acute nephritis of this type, the persistence of the plasma cholesterol above the upper normal limit foretells a chronic course of the disease.

3. In acute nephritis without oedema, the plasma cholesterol is of no diagnostic or prognostic value.

4. In chronic parenchymatous nephritis much higher cholesterol values are frequently found, and the amount of cholesterol increase is in no way proportional to the degree of oedema. In cases of oedema of doubtful origin, a high plasma cholesterol is a strong point in favour of the renal origin of the condition if the other factors which may cause an increased cholesterol content of the blood can be excluded.

5. Renal oedema and the increased plasma cholesterol are not related as cause and effect. They are probably both the result of some toxic process acting upon the tissue cells, particularly those of the reticulo-endothelial system.

6. A persistently raised plasma cholesterol in patients who have been oedema free for a long period is often associated with the early onset of uraemia.

7. In uraemia the cholesterol findings are usually normal or low. Allied to

this group are the toxaemias of pregnancy in which some similar toxic factor frequently causes lower plasma cholesterol figures than would otherwise have been expected.

8. In pure chronic interstitial nephritis the cholesterol is always normal or low. In primary arteriosclerosis, however, higher figures are usually found.

9. The oedema of heart failure is not associated with any increase in the plasma cholesterol unless arteriosclerosis or some other factor be also present.

In conclusion, I wish to thank the Physicians to St. Bartholomew's Hospital for permission to investigate their cases. My thanks are particularly due to Professor F. R. Fraser and to Dr. Geoffrey Evans, to each of whom I am indebted for much helpful advice and criticism.

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A CLINICAL AND METABOLIC STUDY IN OBESITY[1]

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Historical.

Much has been written on the problem of obesity, but it cannot as yet be said that the mechanism by which it is brought about is clear. Du Bois (1) says: 'We do not as yet know why certain individuals grow fat.' This statement must refer especially to those cases in which the onset of obesity cannot be explained solely on the basis of an excess food intake or diminished energy expenditure—that is, so-called endogenous obesity. Of course neither the obese subject nor any other organism can contravene the Laws of the Conservation of Energy and Mass, so that, in the final analysis of the metabolism in obesity, a balance-sheet of energy intake, energy output, and tissue deposition must be possible. This is strongly held by Jones (2), who, from this point of view, rightly attributes every form of obesity to an increase of caloric intake over caloric output. This, we imagine, has never been held in question at all. The older literature is rich in calculations on such a basis. Van Noorden, for example (quoted by Wilder Tileston (3)), calculated that a daily excess consumption of 200 calories, the energy equivalent of a half-pint of milk or of two large oranges, would lead in the course of a year to deposition of 7·8 kg. of fat, or, allowing for the water content of fat tissue, an increase of 11 kg.

The question is not one of the confirmation of the Laws of Energetics, but of the qualitative nature of the metabolism and the quantitative partition of energy.

The delicate regulatory mechanism, by means of appetite and energy expenditure, which makes it possible for a normal individual to maintain his weight practically constant for years, is disturbed in the obese. As Lauter (4) says: 'Exogenous as well as endogenous obesity depends, in our opinion, purely on energy exchanges; on the imbalance between food intake and energy expenditure.' But it is just this faulty ratio and its origin which is the whole problem of obesity.

Once this aberrant metabolic condition sets in, a vicious circle is produced, the energy output by movement and work is diminished, and even on a restricted diet the weight may often remain unchanged or even increase.

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It is rarely that one can attribute obesity to gluttony. Gräfe (5) in his comprehensive monograph says: 'Pure exogenous obesity is probably a very rare disease.' The large majority of obese subjects are found in a class which is not over-endowed with worldly possessions. Many of our patients were hard-working women of the domestic servant and washerwoman class. But even when purely exogenous factors can be claimed as the immediate cause of the obesity, the problem must still remain as to what brought about the lack of energy or the increase of appetite.

A great deal of work has been done to determine if obesity is associated with any definite change in basal metabolism. In exogenous obesity it is uniformly agreed that the basal metabolism calculated on units of surface area is normal (6, 7, 8, 9, 10). Even in cases of extreme obesity Means (11) could detect no characteristic change in basal metabolism.

In obesity due to endocrine disease changes in basal metabolism have been detected. The obesities of hypothyroidism and hypopituitarism are both associated with a reduction of metabolism (12, 13). But it cannot be said that these findings have led to a much greater insight into the mechanism of the condition. It is, for example, true that in a typical myxoedema the reduction in basal metabolic rate is associated with an increase in body weight, but this does not always progress to obesity (see Falta, 14).

In the so-called constitutional obesity distinguished by Strouse (15), in which there is no loss in weight on diets as low as 600 to 1,000 calories per day, the basal metabolic rate is within normal limits.

Boothby and Sandiford (16) examined the basal metabolic rates of 8,614 cases, using the height-weight formula and the Sage standards. They tabulated 94 cases of obesity, of which 81 per cent. were within 10 per cent. of the average normal, 95 per cent. were between -15 per cent. and $+15$ per cent., and 3 per cent. between -20 per cent. and -16 per cent. Efforts have also been made to show that the specific dynamic action of food is lower in obese subjects than in normals, but the results are not convincing. Rahel Plaut (17), by comparing the increase in metabolism after a standard meal given to normal and obese subjects, found a response of from 4 per cent. to 29 per cent. in the obese (12 cases) as compared with 24 per cent. to 52 per cent. in the normals. The results of Gephart and Du Bois (18) and Aub and Du Bois (19) make it probable that Plaut's normal values were considerably too high.

Another view was that of von Bergmann (20), that the obese subject was relatively unable to metabolize fat, and so simply heaped up any fat administered in the food or formed from carbohydrate. Against this is the fact that high respiratory quotients are no more common in the obese than in the normal, and that adipose tissue fat is easily oxidizable.

The concept of *Luxus-Konsumtion* [3] introduced by Gräfe (5) suggested the

[3] By *Luxus-Konsumtion* is meant the power of the normal subject to respond to excessive food intake by an increase in metabolism. It is regarded by Gräfe as the mechanism by which obesity is prevented in the normal.

possibility that obesity might be due to a lack of this 'luxury' response to excess food intake. Whilst this has been demonstrated by Gräfe in dogs, there is no real evidence for it in the obese human subject. If such a lack of *Luxus-Konsumtion* could be demonstrated, then all cases of obesity would become endogenous in the sense that a functional cell disturbance gave rise to the condition.

The question of carbohydrate tolerance and utilization in obesity has received a good deal of attention. It is well established that carbohydrate gives rise to fat in the organism, and that many cases of obesity can be traced to an abnormal addiction to sugar.

Roth (quoted by Tileston (3)) found the blood-sugar increased in 4 out of 16 cases of obesity in the absence of glycosuria. Arnoldi (21) found an abnormally low blood-sugar curve in certain cases of obesity. Joslin, on the basis of 1,000 cases, states that 'the individual who is over-weight is at least twice and at some ages forty times as liable to diabetes as the normal'. Paullin and Sauls (22) found abnormal glucose tolerance in over half of 26 cases of obesity, and claim to have detected five pre-diabetics. Similar results were obtained by John (23). Hagedorn, Holten, and Johansen (24) examined 30 obese patients in regard to diet, exercise, rest, respiratory quotient, and weight, and compared them with 16 normals. They concluded that the obesity was mainly due to an abnormal formation of fat from carbohydrate.

Allison (25) investigated the sugar tolerance of 23 obese patients of the exogenous type, including 8 glycosurics. He found that some show a partial inability to deal with carbohydrate, and that their tolerance is increased if their weight is reduced.

In 1913 Falta argued on theoretical grounds that, for the laying down of fat, actively functioning pancreatic islet-tissue was essential. In 1925 (26) he was able to demonstrate a remarkable increase of weight in three ill-nourished non-diabetic patients, following treatment with insulin and generous carbohydrate diet. The effect was so marked in one patient that she actually became obese. This is an observation frequently made during the treatment of diabetics with insulin, and gives strong evidence of some relationship between the pancreas and obesity. On this point, however, Weber (27) suggests that the relationship may only be apparent, and that we may be dealing with two distinct conditions acting in opposite directions as regards deposition of fats.

The Present Investigation.

The investigations described in this paper were undertaken with a view to determining whether any metabolic differences could be detected between those cases of obesity which are usually classified on clinical and aetiological grounds as exogenous and endogenous.

The metabolic investigations to be reported have been made on a series of 294 cases of obesity. A certain number of them, mostly adults, gave a clearly

defined exogenous history, but the proportion of such cases was surprisingly small. In the majority no clear-cut exogenous history could be obtained, and the obesity was found either to have been present at birth or to have developed at puberty, with the onset of menstruation, or after child-birth or miscarriage, times at which the metabolism is known to be disturbed. Such cases we have classified as endogenous, though we realize that exogenous factors cannot be entirely excluded. In many, no doubt, both factors play a part. Nevertheless, the gain in weight and fat tissue in most of these patients at these times is often so excessive and entirely out of proportion to any alteration in diet or diminution in energy expenditure, that we feel justified in assuming some endogenous change. It has been even more difficult to assess the relative importance of exogenous and endogenous factors in obesity present at birth or developing in early childhood. In the majority of these cases which we have investigated the main factor would appear to be endogenous; in many a strong family history of obesity can be obtained, or the condition would appear to have been transmitted directly from mother to child. In relatively few could the substitution of patent starchy foods for breast-feeding be held responsible for the onset of the condition. On the other hand, it was not unusual to find a history of a mother developing obesity after the birth of a third or fourth child, having previously been thin or of normal proportions, and the child itself showing the same condition. It is difficult, of course, to estimate the influence of exogenous factors in the case of the mother during pregnancy and lactation, but in the case of the child it would seem probable that from this early stage there must be created a tendency to abnormal metabolism. For this reason we have regarded the obesity of such patients as endogenous in type, though we have made no attempt at differentiation in classifying our cases of obesity in children in their earliest years.

The following table shows the classification of our cases, with the percentage number in each group. No cases of well-recognized endocrine syndromes, such as the obesities associated with myxoedema or pituitary tumour, will be reported in this paper. We propose to discuss similar investigations in frank endocrine syndromes in a subsequent communication. We do not wish to infer, however, that endocrine features were not present in some of our cases in the present series, for, in a number of the children in particular, they undoubtedly were. The signs of glandular imbalance, however, were often vague and indeterminate, and we have thought it advisable, in the present state of our knowledge, to adopt a more general classification, and to regard such indications as additional evidence of an endogenous aetiology. This question will be referred to more fully in the following section.

TABLE I.

Total Number of Cases, 294.

Children and Adolescents.

100 cases.

Obese from birth.	Obese from Period of Second Dentition.	Obese from Puberty.
35 %	31 %	34 %

TABLE I (*continued*).

Adults.

Exogenous—45 cases.
33 %.

Endogenous—149 cases.
77 %

Obese from Birth.	Obese from Puberty.	Obesity following Child-birth.
29 %	33 %	38 %

Let us now consider this classification in greater detail. In the *exogenous class* we have grouped those subjects who give a clear history of excessive consumption of food or diminution of energy expenditure, whilst to the endogenous class belong those cases in which no obvious exogenous factor can be detected. On the other hand, in the latter the condition was often present at birth, or developed later at puberty or after child-birth. In many cases a predilection for carbohydrate in large quantities was admitted. In all cases the exogenous factor, when present, was readily elicited in the history. The *endogenous group* we have already discussed to some extent, and given our reasons for regarding those cases which show evidence of obesity from birth as belonging to this class. In the cases which develop at puberty there would seem often some suggestion of dyspituitarism, though without evidence of pituitary tumour. Many show disturbances of growth and menstruation. Particularly common is the association of obesity with overgrowth and early development of the sex characteristics. The onset of obesity is accompanied by marked acceleration of growth, which continues until puberty, when it ceases. Puberty occurs early, at 11 or 12. Bone development is also advanced, and in many cases the epiphyses fuse at this time. The skeleton is large and the bones heavy, and no doubt this is to some extent responsible for the great increase in weight. In girls, menstruation sets in early and may be excessive at the start, though sooner or later there is generally a tendency to oligo- or amenorrhoea. On reaching adult life, these patients tend to get more obese after events such as child-birth, or later at the menopause. On the other hand, many of them are sterile or suffer from repeated miscarriages, the latter also frequently resulting in increasing obesity. The third group of patients with obesity, whom we have included under the endogenous class, are those who develop the condition after child-birth or miscarriage, having previously been of normal proportions or thin. In this group, however, the obesity is seldom so extreme as in the series of patients just mentioned, and there are few, if any, features of endocrine disturbance. An additional point of contrast to the preceding groups is also seen in the absence of any irregularity of menstruation in a very large majority of the patients under discussion. There is, however, one feature which perhaps suggests some endogenous change, and that is, that the condition generally develops after a third or fourth pregnancy, similar, from the point of view of exogenous aetiological factors, to those which have preceded it.

Nevertheless it is possible that the sedentary life associated with repeated pregnancies, and the decreasing energy expenditure of advancing years, play a large part in the genesis of this condition.

Carbohydrate metabolism. To investigate the carbohydrate metabolism in a living animal, one is reduced to a relatively small field of experimental methods. This is also the case in such subjects as obese patients who are ambulatory, and hence not amenable to long metabolism investigation.

No absolutely unequivocal quantitative test for carbohydrate utilization in the living animal exists, and, as we shall point out subsequently, there are cases which on all tests are almost completely intolerant to carbohydrate and yet continue a relatively healthy and undisturbed existence.

As a first method of examination it was decided to employ the well-known glucose tolerance test and the reaction to carbohydrate as manifested by changes in the respiratory exchange and metabolic rate.

The information obtainable by these methods is limited, and, although quantitative data can be calculated, it is questionable as to how far, in the present state of our knowledge, such data present a true picture of the metabolic conditions. Methods of indirect calorimetry can with reasonable care give results in close agreement with those of direct calorimetry, but short-period experiments are not to be relied upon unless, by previous observations on the patient, fairly constant figures are obtained.

In our work the Douglas bag and Rosling valve were used, the analysis being carried out by the Haldane apparatus, and the calculation based on the Zuntz-Schumberg tables for calorie value of oxygen. The patient was in all cases fasted for about fifteen hours and rested on a bed for at least one hour before making a collection. The patient was generally accustomed to the procedure, and no evidence of 'over-ventilation' was obtained. The least evidence of distress on the part of the patient was sufficient for discontinuance of the test until some future period. No calculations of basal metabolic rate were made, as it is impossible to give normal standards for comparison with obese subjects. To calculate on the predicted weight does not help, as the conditions are in no way comparable. Obese subjects with an enormous insulating coat of fat present a case for which there is no real normal standard. In such cases we have therefore contented ourselves with the calculation of the total caloric production per hour and the percentage increase produced by a dose of carbohydrate (glucose).

The increase in heat production produced by a definite dose of sugar is due to the metabolism of the sugar itself, and to a small extent to the stimulus given to the general metabolism by the intermediate products produced during the break-down of the sugar molecule. The period of fasting prior to the investigation of reaction to carbohydrate is of the first importance. This point has been investigated by one of us (M. W. G.) (28) in another connexion. It was found that in the normal subject the tolerance to carbohydrate, as measured by the blood-sugar curve, the presence of glycosuria, and the rise in respiratory quotients following a standard dose of glucose, became progressively lower as the period of

fasting was increased. This point is clearly illustrated in the following table, the figures having been obtained at half-hourly intervals after 50 grm. glucose *per os*. The subject was a normal man of 29 years.

TABLE II.

Period of Fasting	16 Hours.		20 Hours.		40 Hours.	
	Blood-sugar %.	R.Q.	Blood-sugar %.	R.Q.	Blood-sugar %.	R.Q.
Fasting	0·102	0·74	0·081	0·79	0·104	0·73
½ hour	0·150	0·82	0·146	0·77	0·184	0·74
1 hour	0·113	0·88	0·156	0·82	0·187	0·75
1½ hours	0·091	0·90	0·122	0·84	0·141	0·81
2 hours	0·075	0·81	0·100	0·86	0·130	0·78
	No glycosuria		No glycosuria		Glycosuria	

There is thus no doubt of the necessity of a standard period of fasting before the test is carried out. Indeed, after forty hours' fasting, a picture closely analogous to that of mild diabetes can be obtained in the normal subject.

In choosing a period of fifteen hours' fasting prior to examining the metabolism of our cases we follow the usual practice, but it must be realized that the condition is by no means basal after such a time. In fact, the heat production cannot be regarded as truly basal until all effects from previously ingested food, particularly protein, have been removed. This probably does not occur until after two days of starvation. The term 'basal metabolism' as at present used, viz. the metabolism measured from twelve to eighteen hours after food, can only be regarded as an arbitrary standard. For ambulatory cases such a period is convenient, and any much longer one impracticable. Moreover, from the above table, it would appear that an attempt to obtain truly basal figures would involve complications at present not easy to understand.

Respiratory quotient. A further matter to which attention must be drawn is the occurrence and interpretation of respiratory quotients greater than unity. Such quotients indicate that in some way carbohydrate metabolism is proceeding with a conservation of oxygen—that is, that in some way intra-molecular oxygen is being used rather than inspired oxygen, or, in other words, that oxygen-poor substances are being formed from oxygen-rich carbohydrate. The existence of respiratory quotients greater than unity in carbohydrate-fed animals, which are certainly laying down fat, has led to the view that such respiratory quotients indicate a change from carbohydrate to fat. This reaction is exothermic, but the liberation of energy is very slight. The extra CO_2 liberated over and above the O_2 utilized represents a certain amount of fat formed from carbohydrate. The following equation, taken from Lusk (29) and quoted from Bleibtreu's work, shows this:

$$\underset{997{\cdot}2\text{ calories}}{270{\cdot}6\text{ grm. glucose}} \rightarrow \underset{950{\cdot}0\text{ calories}}{100\text{ grm. fat}} + 115{\cdot}45\text{ grm. } CO_2 + 54{\cdot}6\text{ grm. } H_2O.$$

Remembering that the molecular volume is 22·4 litres, and the molecular weight of CO_2 is 44, we have:

$$1 \text{ litre of } CO_2 \text{ thus liberated} = \frac{997{\cdot}2 - 950{\cdot}0}{115{\cdot}45} \times \frac{44}{22{\cdot}4} = 0{\cdot}803 \text{ cal.}$$

This equation is applied to the CO_2 produced in excess of that required to give a respiratory quotient of unity, and the calories thus determined added to the value obtained by calculating on a respiratory quotient of unity. The correction thus introduced is usually very small. The following case, which showed a very marked rise in respiratory quotient above unity, illustrates this. The results were obtained immediately before, and at half-hourly intervals after, a dose of 30 grm. glucose in a male cretin of 10 years, fifteen hours after food and under hospital conditions.

TABLE III.

Time after Sugar.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hour. Uncorrected.	Calories per Hour. Corrected.	Fat formed per Hour. Grm.
0	0·087	0·904	85·7	77·5	23·35	23·35	0
½	0·085	1·00	81·7	81·7	24·75	24·75	0
1	0·133	1·07	77·5	82·9	23·47	23·73	0·554
1½	0·125	1·16	78·8	91·4	23·87	24·47	1·288
2	0·099	1·155	77·0	88·95	23·33	23·91	1·219

The last column above represents the fat formation per hour calculated from the equation, 100 grm. fat formed from sugar = 115·45 grm. CO_2 liberated; the rate of fat formation in this case is seen to be very considerable. Such figures are rarely found even in very obese patients, a fact which is significant, seeing that there can be no doubt that in many cases the source of the fat was certainly carbohydrate.

The blood-sugar curve. The blood-sugar curve is now well established in metabolic work, and it is, perhaps, the best test for carbohydrate storage. Normal, diminished, or increased power of storing carbohydrate are judged to exist according to the rapidity with which the blood-sugar returns to normal values after an arbitrary dose of sugar, usually 50 or 75 grm. of glucose, administered about fifteen hours after food. The following are curves obtained from obese subjects:

Time in Hours.	0	½	1	1½	2
Normal tolerance	0·100	0·167	0·157	0·129	0·092
Increased tolerance	0·072	0·113	0·133	0·115	0·096
,, ,,	0·085	0·106	0·117	0·083	0·104
Decreased tolerance	0·198	0·223	0·272	0·380	0·288
Intermediate type	0·114	0·192	0·135	0·135	0·136
,, ,,	0·147	0·192	0·192	0·156	0·147

The curves of increased tolerance in which the rise in blood-sugar is very slight must not be interpreted as indicating diminished absorption. It must be remembered that even in normal cases the fall in blood-sugar to fasting levels occurs at a time when it can easily be shown that large quantities of sugar are still present in the stomach and there is no reason to suppose that there is any diminution in the rate of absorption. Indeed the period of most active oxidation of sugar can be shown to take place, as a general rule, after the maximum blood-sugar has been passed. In those cases in which curves of markedly diminished

tolerance were obtained it could be shown that active oxidation of sugar was proceeding, and further that it was in such cases that the best rises in respiratory quotient could be demonstrated. Indeed we are led to suppose that, when the blood-sugar curve shows minimal rises, the organism is in a position to respond immediately to administered carbohydrate by a copious secretion of insulin and an extremely rapid storage and oxidation of sugar.

It must, however, be pointed out that low blood-sugar curves may also be obtained in cases of malnutrition due to very poor powers of absorption. But such considerations did not enter into our cases with very low blood-sugar curves, as they were all very obese.

Findings in Obesity.

A. *Exogenous obesity.* In giving our results in obese cases, we will first present the blood-sugar findings in those cases in which no factors other than gross overeating, sedentary habits, addiction to large amounts of carbohydrate, and similar influences seem to enter. Evidence of endocrine disturbance was not found in these cases, and they may hence be regarded as of the exogenous class. The cases have been grouped according to age, and the curves were obtained after 50 grm. of glucose.

TABLE IV.

				Hours after Glucose.				
No.	Weight. st.	lb.	Age.	0	½	1	1½	2
Age Group up to 30 Years.								
1	14	12	21	0·086	0·177	0·109	0·087	0·086
2	13	12	22	0·110	0·156	0·181	0·119	0·109
3	—		26	0·100	0·154	0·204	0·216	0·194
4	13	6	27	0·113	0·187	0·109	0·081	0·100
5	7	12	13	0·104	0·177	0·129	0·104	0·081
6	14	2	18	0·083	0·166	0·117	0·095	0·077
7	14	8	26	0·104	0·191	0·109	0·085	0·081
Age Group 30 to 40 Years.								
1	13	10	34	0·129	0·197	0·177	0·156	0·156
2	12	13	40	0·114	0·210	0·160	0·137	0·119
3	10	7	39	0·104	0·201	0·177	0·127	—
4	13	5	31	0·089	0·144	0·186	0·192	0·150
5	15	0	33	0·085	0·113	0·100	0·090	—
6	18	0	40	0·100	0·165	0·120	0·090	—
7	12	3	39	0·122	0·142	0·188	0·155	0·114
8	12	8	37	0·100	0·168	0·181	0·153	0·130
9	12	7	38	0·112	0·162	0·188	0·119	0·112
10	10	4	32	0·109	0·152	0·146	0·115	0·112
11	11	10	39	0·109	0·137	0·129	0·106	—
12	20	0	30	0·102	0·120	0·159	0·115	0·113
13	20	0	35	0·092	0·162	0·100	0·085	0·100
Age Group 40 to 62 Years.								
1	13	5	56	0·137	0·172	0·252	0·162	0·147
2	16	10	41	0·111	0·217	0·238	0·204	0·155
3	11	10	42	0·097	0·181	0·137	0·071	0·054
4	15	8	50	0·122	0·197	0·210	0·188	0·138
5	15	6	45	0·120	0·168	0·229	0·209	0·160
6	15	0	45	0·117	0·156	0·129	0·129	0·117
7	17	10	53	0·106	0·181	0·201	0·149	0·118
8	16	7	62	0·104	0·170	0·168	0·143	0·141
9	12	4	48	0·109	0·179	0·152	0·100	0·081

The first thing which strikes us in these results is the very normal values for the fasting blood-sugar. Whatever further conclusions may arise from the other blood-sugar values, the fact that of the 29 cases here presented only four show a fasting blood-sugar greater than 0·120 per cent. is sufficient indication that we are not dealing with any profound disturbance as far as blood-sugar is concerned.

Further examination of these curves shows that at the first half-hour 13 have exceeded 0·170 per cent., at the hour 13 are greater than 0·170 per cent., at one and a half hours 4 are above 0·170 per cent., and after two hours only 9 have not yet returned to fasting levels. Of the series, 20 cases have at some time or other exceeded 0·170 per cent., and almost all of these showed glycosuria during the test.

We are led, then, to the view that these cases show a temporary delay in the power of storing carbohydrate, but this is rapidly readjusted. It is to be noted that Case No. 5 in the age group 30 to 40, which shows a markedly increased tolerance to sugar, had been treated with thyroid extract prior to this investigation. Excluding this case, it is seen that in no other does increased tolerance occur. In fact, increased tolerance to sugar is practically never met with in cases of obesity from which endocrine influences can be excluded clinically.

This diminished rapidity in storing carbohydrate has its counterpart in the findings in animals, when the glycogen content of the liver runs inversely to the fat content.

The existence of many perfectly normal blood-sugar curves in cases of extreme exogenous obesity shows that any all-embracing conclusion in this direction is impossible. The mechanism for storing sugar may, in spite of years of gross abuse, still remain quite efficient in some cases, whilst in others it easily becomes damaged. Years of indulgence and inactivity may lead to a marked intolerance to glucose, as is shown in the following cases:

Patient No.	Weight. st.	lb.	Age.	Blood-sugar Percentages after 75 grm. Glucose. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	2½ hrs.
1	12	7	36	0·139	0·154	0·209	0·190	0·181	—
2	12	0	28	0·097	0·179	0·156	0·156	0·137	—
3	22	0	40	0·097	0·164	0·179	0·166	0·136	—
4	15	7	45	0·120	0·168	0·229	0·209	0·160	0·094

Such cases of exogenous obesity, showing as they do a glycosuria after administration of glucose, must be distinguished from true diabetes. In these cases, as a general rule, there is not an inability to metabolize carbohydrate as judged by a rise in respiratory quotients and increase in heat production. Further, there is no apparent interference with fat metabolism, in that there is no appearance of ketosis in anything more than the merest traces of abnormal acids in the urine.

There seems to be little doubt that we are here dealing with a deficiency in the power to store carbohydrate.

The following results indicate that these cases of exogenous obesity do not show any diminution in the power to oxidize sugar:

EXOGENOUS OBESITY.

I. Mrs. O., aged 36. Normal till marriage, since married gained 2½ stone in 4–5 years. Sedentary life. Menstruation regular. 75 grm. glucose at 11.0.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
11.0	0·139	0·68	229	156	64·5	—
11.25	0·154	0·71	257	182	72·3	+12·1
11.55	0·209	0·82	222	182	64·1	—
12.25	0·190	0·84	213	178	62·0	−3·9
1.25	0·181	0·80	198	159	57·0	−11·6

II. Mrs. L., aged 28. Normal till 3 years ago when married. After marriage took less exercise and gained in weight from 8½ to 12 stone—a gain of 3½ stone in 3 years. Menstruation regular. 75 grm. glucose at 11.47.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.45	0·097	0·75	260	195	74·0	—
11.17	0·179	0·75	311	234	88·6	+19·7
11.48	0·156	0·94	304	285	90·6	+22·4
12.21	0·156	1·06	214	227	64·7	−12·6
12.51	0·137	0·78	177	138	50·7	−31·5

III. Mrs. B., aged —. 22 stone. 75 grm. glucose at 11.10.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
11.10	0·097	0·82	301	246	87·0	—
11.51	0·164	0·73	362	264	102·4	+17·6
12.27	0·179	0·84	349	294	101·7	+16·8
12.55	0·166	0·924	333	308	99·0	+13·7
1·28	0·136	0·86	312	269	91·3	+4·3

IV. Mrs. B., aged 45. 15½ stone. Obesity 8 years, since acquisition of confectionery business; previously normal. Menstruation regular. 75 grm. glucose at 10.44.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.43	0·120	0·76	297	226	79·2	—
11.23	0·168	0·74	300	222	85·2	+7·6
11.53	0·229	0·83	312	259	90·7	+14·5
12.32	0·209	0·87	295	257	86·4	+9·2
12.50	0·160	0·87	204	178	59·9	+24·3
1.23	0·094	—	—	—	—	—

For comparison we give results in a normal case, aged 30, weight 11 stone.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.45	0·102	0·76	177	135	50·5	—
11.16	0·150	0·82	189	155	54·8	+8·5
11.46	0·113	0·875	187	164	55·0	+8·9
12.16	0·091	0·90	176	158	52·1	+3·2
12.45	0·075	0·81	149	121	42·9	−13·0

These figures make it clear that in the case of exogenous obesity in which markedly abnormal blood-sugar curves are obtained, the metabolic picture may show that oxidation of sugar is not less rapid than in the normal. Many more such results should be given, but the above figures are typical. It will be observed that the maximum rise in respiratory quotient generally occurs during the fall in blood-sugar. The fall below the basal calorie production has been very frequently observed, and it would seem that at such times the storage mechanism for carbohydrate is at its height.

B. *Endogenous obesity.* The type of case which we will deal with under this heading has already been described in the early part of this paper. It must again be emphasized, however, that no cases of gross endocrine disturbance are included. The cases fall into three main groups, i.e.: (1) those developing obesity at birth, (2) at puberty, (3) following child-birth. As in the exogenous cases, it will again be convenient to discuss the carbohydrate metabolism under the divisions of age groups.

TABLE VI.

Age Group up to 20 Years. Blood-sugar after 50 grm. Glucose ½-hourly.

Patient.	Age.	Onset of Obesity.	Weight. st.	lb.	0	½	1	1½	2
1	14	Birth	23	0	0·084	0·106	0·103	0·120	0·126
2	9	At 7	8	4	0·072	0·088	0·120	0·095	0·100
3	16	At 9	18	0	0·085	0·106	0·117	0·083	0·104
4	13	Puberty	10	7	0·072	0·113	0·133	0·115	0·096
5	13	At 8	13	9	0·079	0·118	0·128	0·125	0·125
6	15	At 10	16	7	0·087	0·121	0·123	0·152	0·118
7	17	Birth	12	8	0·087	0·129	0·146	0·131	0·109
8	14	At 5	—		0·102	0·117	0·117	0·120	0·106
9	17	Puberty	15	6	0·092	0·097	0·115	0·129	0·111
10	17	Birth	18	11	0·122	0·129	0·137	0·129	0·124
11	16	Birth	—		0·062	0·129	0·129	0·090	0·100

These cases were all very obese, and the onset of the condition occurred at an early age. A family history of obesity could in general be elicited, and some of the patients were known to be inordinately addicted to carbohydrate. In spite of this exogenous factor, the mechanism for dealing with sugar was so powerful that the blood-sugar curves are in practically all the cases of the high tolerance type.

By simultaneous examination of the respiratory exchange in these cases we satisfied ourselves that there was no question of improper absorption. We give two cases showing this.

ENDOGENOUS OBESITY.

I. H. W., aged 13. Obesity from birth. Strong family history of obesity on mother's side. Weight 10 st. 7 lb. 50 grm. glucose at 10.10.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.
10.05	0·097	0·78	273	213	78·2
10.44	0·111	0·765	295	226	84·27
11.15	0·113	0·83	269	224	78·2
11.44	0·139	0·82	276	227	80·1
12.16	0·117	0·90	281	253	83·13

II. D. F., aged 9. Obesity for 2 years following removal of tonsils. Weight 8 st. 4 lb. 50 grm. glucose at 10.50.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.
10.50	0·104	0·82	243	198	70·2
11.24	0·137	0·93	253	235	75·4
11.53	0·111	0·91	253	230	75·1
12.23	—	0·91	230	210	68·2
12.53	0·111	0·95	226	215	67·7

As in all cases of obesity, a direct demonstration of respiratory quotients exceeding unity after feeding carbohydrate is rare. Of the formation of fat from carbohydrate in these cases there can be no doubt but its demonstration by indirect methods is in these cases very difficult. The trouble probably lies in our present interpretation of the respiratory exchange. There is no certainty that non-protein respiratory quotients between 0·7 and unity do not admit of another interpretation than simple combustion of various proportions of carbohydrate and fat. In a recent paper Cathcart and Markowitz (30) take the view that every respiratory quotient represents a dynamic equilibrium involving oxidation of carbohydrate and transformation of fat to carbohydrate and carbohydrate to fat. Thus, a change in respiratory quotient represents a shift of metabolism in the direction of one or other of the reactions carbohydrate$\rightleftarrows$fat or towards greater oxidation of carbohydrate. On such a view the absence of respiratory quotients exceeding unity in obese subjects, even after administration of alpha-beta glucose, is to be explained by the masking effect of the simultaneous utilization of fat for energy purposes.

The high tolerance to carbohydrate seen in these cases of early endogenous obesity is practically never met with in the later decades of life, and our evidence is all in favour of the view that this high tolerance gives place in the passage of years to a definitely diminished tolerance. This process is a gradual one, and we propose to demonstrate it by giving the next group of cases of endogenous obesity, which show exactly similar clinical and family histories to those in the age-group up to 20 years, but were first observed at a later stage of the process. Twelve cases of obesity following child-birth are included as of endogenous origin.

ENDOGENOUS OBESITY.

Adults: (*a*) obesity from birth; (*b*) obesity from puberty; (*c*) obesity following child-birth.

Table VII.

Age Group 20 to 40 Years. Blood-sugar after 50 grm. Glucose ½-hourly.

Patient.	Age.	Onset of Obesity.	Weight. st.	lb.	0	½	1	1½	2
(*a*) 1	37	Birth	16	3	0·100	0·167	0·167	0·120	0·092
2	31	„	20	10	0·110	—	0·152	0·135	0·129
3	22	„	11	5	0·114	0·192	0·135	0·135	0·136
4	27	„	16	0	0·106	0·120	0·125	0·106	0·086
5	36	„	12	9	0·104	0·211	0·197	0·166	0·152
6	33	„	17	1	0·110	0·221	0·227	0·172	0·152
7	33	„	14	0	0·071	0·095	0·080	0·123	0·087
8	36	„	17	2	0·089	0·098	0·142	0·171	0·192
9	39	„	12	10	0·147	0·192	0·192	0·156	0·147
10	32	„	18	7	0·092	0·135	0·133	0·125	0·125

TABLE VII (*continued*).

Patient.	Age.	Onset of Obesity.	Weight st.	lb.	Blood-sugar after 50 grm. Glucose ½-hourly. 0	½	1	1½	2
11	31	Birth	14	2	0·092	0·137	0·118	0·104	0·102
12	32	,,	—		0·118	0·122	0·134	0·134	—
(*b*) 13	39	Puberty	21	0	0·134	0·172	0·197	0·210	0·231
14	37	,,	14	0	0·129	0·172	0·197	0·192	0·172
15	39	,,	—		0·100	0·156	0·129	0·083	0·087
16	33	,,	—		0·098	0·102	0·125	0·120	0·098
17	35	Following child-birth, previously thin	15	10	0·122	0·130	0·152	0·112	0·115
18	39	,,	15	13	0·129	0·156	0·181	0·212	0·213
19	33	,,	14	7	0·120	0·162	0·201	0·209	0·193
20	31	,,	14	0	0·103	0·131	0·194	0·139	0·135
21	33	,,	12	12	0·121	0·156	0·156	0·156	0·169
22	38	,,	15	4	0·080	0·135	0·186	0·156	0·120
23	20	,,	12	10	0·144	0·200	0·188	0·181	0·162
24	37	,,	15	12	0·075	0·156	0·152	0·113	0·085
25	37	,,	14	10	0·112	0·133	0·118	0·087	0·112
26	35	,,	15	4	0·110	0·131	0·142	0·142	0·128

Analysis of this group shows that 9 cases give curves of normal tolerance, 7 cases increased tolerance, and 10 cases diminished tolerance as far as storage power is concerned.

The following tables taken at random from among the metabolic analyses of these cases show that oxidation of sugar in these cases is efficient.

I. Example of *Obesity developing at Puberty*—patient first seen at age of 32.

Mrs. A., aged 32. Normal child. Obesity first developed at puberty with onset of menstruation. Menstruation always regular. Obesity much exaggerated after marriage and child-birth. Strong family history of obesity. Weight 14 st. 6½ lb. 75 grm. glucose at 10.30.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.30	0·090	0·76	296	225	84·3	—
11.05	0·141	0·82	312	287	90·4	+7·2
11.35	0·150	0·87	299	260	87·6	+3·9
12.05	0·133	0·89	271	241	79·9	−5·2
12.35	0·133	0·81	259	210	84·8	−11·3

II. Example of *Obesity developing after Child-birth*—patient previously thin. First seen at age of 21.

Mrs. L., aged 21. Thin until child-birth 18 months ago. Nursed child for 9 months and subsequently gained 4 st. in weight in following 9 months. Menstruation regular. Weight 12 st. 11 lb. 75 grm. glucose at 10.18.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.16	0·095	0·84	222	186	64·6	—
10.52	0·134	0·92	254	234	75·5	+16·9
11.16	0·142	1·05	247	259	74·8	+15·8
11.45	0·134	0·95	229	218	68·6	+6·2
12.15	0·137	0·94	164	154	49·0	−24·1

III. Example of *Obesity following Child-birth.*

Mrs. D., 21 stone. Endogenous obesity (following child-birth). Aged 39. Thin until marriage at 18. Obesity developed after birth of first child at age of 19, exaggerated by succeeding pregnancies; increase in weight from 11 stone to 21 stone. Family history of obesity. Sister also became obese after child-birth. 75 grm. glucose at 11.20.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
11.20	0·106	0·82	303	249	87·8	—
11.55	0·166	0.81	320	260	92·6	+5·4
12.28	0·236	1·06	305	323	92·3	+5·2
1·0	0·240	0·86	256	220	74·8	−14·8
1.35	0·206	0·87	276	240	80·9	−7·8
2.15	0·201	—	—	—	—	—
2.45	0·156	—	—	—	—	—

When we present the blood-sugar findings in cases of endogenous obesity of ages greater than 40, it will be at once appreciated that a different state of things exists.

ENDOGENOUS OBESITY.

(*a*) Obesity from birth; (*b*) obesity from puberty; (*c*) obesity following child-birth.

TABLE VIII.

Age Group 49 and over. Blood-sugar after 50 grm. Glucose ½-hourly.

Patient.	Age.	Onset of Obesity.	Weight. st.	lb.	0	½	1	1½	2
(*a*) 1	46	Birth	17	3	0·137	0·177	0·192	0·202	0·188
(*b*) 2	46	Puberty	17	4	0·198	0·223	0·272	0·380	0·288
3	57	,,	17	2	0·188	0·231	0·312	0·272	0·292
4	42	,,	15	0	0·104	0·142	0·177	0·157	0·142
5	58	,,	12	7	0·147	0·192	0·217	0·232	0·222
6	49	,,	—		0·160	0·264	0·325	0·420	0·360
7	59	,,	17	2	0·113	0·162	0·181	0·175	0·141
8	51	,,	—		0·085	0·133	0·133	0·115	0·098
(*c*) 9	44	Following child-birth, previously thin	14	7	0·102	0·150	0·156	0·130	—
10	47	,,	13	10	0·172	0·231	0·178	0·178	0·181
11	49	,,	14	6	0·118	0·134	0·187	0·192	0·187
12	46	,,	13	7	0·134	0·192	0·256	0·181	0·152
13	46	,,	18	0	0·107	0·137	0·202	0·134	0·090
14	43	,,	13	8	0·100	0·131	0·117	0·086	0·089
15	51	,,	14	0	0·112	0·131	0·194	0·200	—
16	56	,,	13	10	0·137	0·172	0·202	0·162	0·147

Examining this group we find that only four show curves of normal tolerance, two increased, and the remainder markedly diminished tolerance. Increased tolerance is not frequently met with in these cases of advanced endogenous obesity, even two in sixteen giving rather an exaggerated idea of its occurrence.

As far as oxidation of sugar is concerned, it may be said that many show perfectly efficient response, whilst others, though giving a good rise in respiratory quotient, tend to keep their heat production steady even after administration of sugar. The following cases illustrate this latter point:

I. Mrs. T., aged 50. Endogenous obesity first developed at puberty with onset of menstruation. Married and has 2 children. Menopause at 44. Menstruation previously regular. Strong family history of obesity. Weight 17 st. 2 lb. 75 grm. glucose at 10.35.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.53	0·104	0·76	213	162	60·8	—
11.10	0·179	0·77	202	155	57·6	−5·26
11.39	0·179	0·81	206	167	59·5	−2·1
12.8	0·184	0·88	201	177	59·2	−2·1

II. Mrs. W., aged 50. Endogenous obesity first developed at puberty with onset of menstruation, exaggerated after miscarriage at age of 36. Menstruation very irregular (amenorrhoea) as girl. Sterility—three miscarriages. Strong family history of obesity. Weight 17 st. 4 lb.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
10.24	0·120	0·80	237	190	68·2	—
10.59	0·131	0·80	237	190	68·3	0·0
11.27	0·175	0·86	235	202	68·5	0·0
11.58	0·191	0·87	236	205	69·1	+1·3
12.28	0·191	0·86	231	199	67·7	−0·8

In neither of these two cases did the sugar produce any rise in heat production, although a marked rise in respiratory quotient took place. It would be dangerous to dogmatize on these figures, but they provide presumptive evidence of less power to deal with sugar than any of the other groups of endogenous obesity.

What would appear to be a still more advanced stage of this condition is occasionally met with, and the two following cases are given as examples. In these patients, not only is the storage apparatus less efficient than normal, but the oxidative mechanism is also affected.

I. Mrs. B., aged 59. Weight 15 st. 1 lb. 75 grm. glucose at 11.00.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
11.00	0·152	0·71	224	159	62·0	—
11.30	0·222	0·77	206	159	58·9	−5·0
12.00	0·181	—	—	—	—	—
12.30	0·199	0·81	207	168	60·0	−3·2
1.00	0·202	0·77	203	156	58·0	−6·4
1.30	0·203	—	—	—	—	—

Such a picture is one which one expects to find in a mild diabetic, but as a matter of fact this patient had no signs of diabetes at all, except a glycosuria. That this type of case is essentially different from the diabetic will be discussed more fully in a future communication, in which we will show that, with appropriate treatment, both the blood-sugar curves and caloric production can be made to approach the normal very closely. What exactly is at fault in such patients is very hard to say in the present state of our knowledge.

The following case appears to be in an even more advanced stage of this condition:

II. Mrs. V., aged 50. 16 st. Obesity since birth, subsequently lost much weight at age of 20, the result of tuberculosis. Since age of 30 steadily gained—to 16 st. at the present time. Strong family history of obesity.

Time.	Blood-sugar %.	R.Q.	O_2 per Min. c.c.	CO_2 per Min. c.c.	Calories per Hr.	Percentage Difference from Basal Calories.
11.52	0·336	0·84	258	216	74·9	—
12.30	0·327	0·82	255	209	73·8	−1·5
1.00	0·396	0·795	255	203	73·3	−2·1
1.33	0·400	0·747	275	205	78·0	+4·1
1.40	0·376	—	—	—	—	—
1.00	0·312	—	—	—	—	—

On the face value of this table one would say this patient was diabetic. In fact, however, she was gaining weight, had no ketosis, and was quite well except for a certain amount of vulvitis due to intense glycosuria. This and the former patient were excreting large quantities of sugar, and on the modern theory of keto-antiketogenesis should have shown strong ketonuria. There appears in such cases to exist an adaptation to a type of metabolism not primarily dependent on carbohydrate.

Experiments on rats could be adduced to show that it is possible to reach a stage when the production of ketone bodies by excessive fat ingestion begins to fall steadily, showing a definite adaptation to a fat-type of metabolism. In our cases of obesity showing such high intolerance to carbohydrate without any accompanying ketosis, it is reasonable to suppose that we are dealing with an adaptation to a type of metabolism which can proceed satisfactorily without much carbohydrate. This type of metabolism may continue for years before any evidence of failure begins to appear. When, in addition to the carbohydrate intolerance, the fat mechanism fails, the condition may go over into that of diabetes.

Summary and Conclusions.

1. A large number of cases of obesity have been investigated as to their carbohydrate metabolism, using the method of the blood-sugar curve and the respiratory exchange.

2. The cases have been broadly divided into exogenous and endogenous types according to the clinical history. In grouping the endogenous cases, careful attention was paid to family history, menstrual history, and any other details which confirmed the diagnosis of endogenous obesity. These latter cases included those whose obesities dated from birth, puberty, or followed child-birth. No cases of gross endocrine disturbance have been included.

3. In exogenous obesity it was found that the tolerance to glucose was normal or diminished, and practically never increased. By grouping according to age a process of continuous diminution in carbohydrate tolerance could be

detected, leading in some cases to an extreme intolerance with glycosuria. Oxidation, however, was in general good, and it would seem that in these latter patients we are dealing with an extreme deficiency in the power to store carbohydrate.

4. In endogenous cases a similar continuous process of diminution of sugar tolerance could be made out. By age grouping it was found that endogenous cases under 20 years of age almost all showed increased carbohydrate tolerance with excellent oxidation. Between the ages of 20 and 40 increased, normal, and diminished tolerance were about equally frequent. Above 40 years diminished tolerance predominated, though oxidation of sugar was quite good. Nevertheless, respiratory quotients exceeding unity were very rare. In the extreme cases, however, oxidation was defective.

5. In both exogenous and endogenous obesity a condition is established in which there is a diminution in the power to store carbohydrate. Both in the exogenous and the majority of the endogenous cases, however, there is no marked diminution in oxidizing power. In the extreme cases of the endogenous type, as has already been mentioned, oxidation is definitely defective. Another distinction between the two conditions seems to be that the frankly endogenous case starts its career with an increased tolerance.

6. Whether the diminished storage power in these patients is primary or secondary to the obesity it is difficult to say. It appears to be secondary in exogenous obesity, but in endogenous cases the young patient shows, as we have seen, a very much increased tolerance. How far the internal secretion of the pancreas may be responsible for the condition in early endogenous cases is a matter for further investigation. That there is a close connexion between obesity and certain cases of diabetes has long been observed, and our cases tend to show how the diabetic condition is gradually approached through the passage of years.

7. As a final summary it may be said that the only distinction from the point of view of carbohydrate metabolism which can be drawn between cases grouped clinically and aetiologically as exogenous and endogenous is that, in the early stages of the endogenous, there exists a markedly increased carbohydrate tolerance, both as regards storage and oxidation, which does not exist in the exogenous. In the intermediate and later stages of both varieties, no clear differentiation can be drawn between their metabolism of carbohydrate, though it would seem that in the late stages of endogenous obesity there is a tendency towards a more extreme intolerance to carbohydrate, with an approach to a picture which may resemble diabetes.

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A STUDY OF THE PROTECTIVE ACTION OF SERUM AGAINST HAEMOLYSIN IN CASES OF DIPHTHERIA[1]

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It is an established fact that serum has an inhibitory effect on various haemolysins. Ransom (1), Ford (2), Bayer (3), Noguchi (4), von Liebermann (5), Lüdke (6), Sellards (7), Moss and Barnes (8), Lamar (9), Clark and Evans (10), Ponder (11), and Donnelly and Mitchell (12), using different haemolysins, either bile-salts, oleic acid, or saponin, demonstrated quite definitely the above-stated fact. The portion of the serum which is responsible for this inhibitory effect has been much discussed. Simon, Melvin, and Roche (13) believed that the chief part in the antihaemolytic powers of the serum was played by cholesterol. Clark and Evans (10), however, showed that while extraction of serum by ether and removal of lecithin and cholesterol diminished the antihaemolytic properties, the serum was still antihaemolytic. Clark, Zenck, and Evans (14) showed that treatment of the serum which altered the physical state or removed all or part of the proteins diminished the protective power of the serum. Ponder (11) working chiefly with saponin came to the conclusion that the inhibition was probably due to the formation of a loose physical compound in the nature of an adsorption reaction between the lysin and the serum proteins. Donnelly and Mitchell (12) came to a similar conclusion.

The importance, clinically, of this property of serum is that in certain diseases this antihaemolytic effect is markedly impaired. Several observers, Dietrich (15), Kahn and Potthoff (16), Lundwall (17), Weis-Ostborn and Silberstern (18), have shown that in carcinoma there is a marked reduction of this antihaemolytic property, and that this property can be made use of in the diagnosis of doubtful cases, provided other factors such as febrile conditions bringing about diminution of this property are eliminated. Simon, Melvin, and Roche (13) found that in cases of syphilis and tuberculosis the protective action of the serum against saponin was diminished.

Clark and Evans (19) showed that in anaemias, especially of the haemolytic type, there was a marked impairment of this antihaemolytic property.

[1] Received October 10, 1927.

It occurred to us that it might be useful to investigate this phenomenon in diphtheria, especially from the point of view of prognosis, as to its relationship with paralysis, and possibly as an indication for treatment. As our haemolysin we used a 1 per cent. solution of ricinoleate in normal saline. We used sodium ricinoleate in preference to other haemolysins because of its formation of true solutions (Larson (20)). The patients were bled from the arm and the serum separated. The serum was tested as soon as possible on the same day, being kept in the refrigerator till required. The test was carried out in the following way: To each of three narrow tubes were added 0·5 c.c. of the patient's serum and to three other tubes 0·5 c.c. of a healthy person's serum. To tube 1 was added 0·1 c.c. of 1 per cent. sodium ricinoleate, to tube 2, 0·2 c.c., and to tube 3 was added 0·3 c.c. The mixtures were shaken and allowed to stand at room temperature for half an hour. Then 0·2 c.c., 0·1 c.c., and 0·05 c.c. were taken from each tube and added to 0·5 c.c. of 3 per cent. suspension of ox blood-cells. These were put in the incubator at 37° C. for one hour and then the varying degrees of haemolysis were read.

Cases were specially chosen which from the clinical point of view would be likely to develop paralysis. These were classified according to the amount of exudate present in the throat.

\+ indicates membrane on the fauces alone.

\+ + indicates membrane on the fauces extending over the uvula.

\+ + + indicates membrane of fauces, uvula, and palate.

Samples of blood were taken from patients as far as possible before antitoxin was given, after antitoxin was given, before the onset of paralysis, and during the period of paralysis.

Case Reports.

Case 1. F. H. T., aged $6\frac{9}{12}$ years. Admitted third day of illness. Exudate + +.

Serum.	Day of Illness.	c.c. of 1% Sodium Ricinoleate to 0·5 c.c. Serum. 0·1			0·2			0·3		
		c.c. of Mixture.								
		0·2	0·1	0·05	0·2	0·1	0·05	0·2	0·1	0·05
		I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.*
F. H. T.	3	–	–	–	++++	++	–	++++	++	–
Control		–	–	–	–	–	–	++	+	–
Before antitoxin was given; shows lack of protection.										
F. H. T.	5	–	–	–	+++	++	–	++++	++	–
Control		–	–	–	–	–	–	++	+	–
After 30,000 units of antitoxin; still lack of protection.										

* In the subsequent tables the tubes I–IX contain the same proportions of ricinoleate and serum as in Table I and the degrees of haemolysis are indicated in the same way.

++++ = Complete haemolysis.
+++ = Almost complete haemolysis.
++ = Partial haemolysis.
\+ = Trace of haemolysis.
– = No haemolysis.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
F. H. T.	13	–	–	–	+	–	–	++++	+++	–
Control		–	–	–	–	–	–	++++	+++	–

Practically no lack of protection.

F. H. T.	29	–	–	–	–	–	–	++++	++	+
Control		–	–	–	–	–	–	++++	++	+

No lack of protection.

Table I. This case did not develop paralysis and was discharged cured. The throat cleared early. The lack of protection was present before antitoxin was given and just after, but there was no lack of protection on the thirteenth day or afterwards.

Case 2. D. D., aged $4\frac{2}{12}$ years. Admitted on seventh day of illness. Exudate + +.

D. D.	7	–	–	–	++	–	–	++++	++++	+
Control		–	–	–	–	–	–	++++	+++	–

Before antitoxin; slight lack of protection.

D. D.	12	++++	++	+	++++	++++	++	++++	++++	+++
Control		–	–	–	++	+	–	++++	++++	++

After 20,000 units of antitoxin; marked lack of protection.

D. D.	21	++++	+	–	++++	++++	–	++++	++++	++++
Control		–	–	–	–	–	–	++++	++++	++

Still lack of protection.

D. D.	38	–	–	–	+	–	–	+++	+	–
Control		–	–	–	+	–	–	+++	+	–

No lack of protection.

Table II. This patient did not develop paralysis and completely recovered. The long period of lack of protection was probably due to delayed treatment, which was not given till the seventh day, thus allowing more complete permeation of toxin. The injection of more antitoxin might possibly have shortened the period of lack of protection.

Case 3. K. M., aged $5\frac{1}{2}$ years. Admitted on sixth day of illness. Exudate +.

K. M.	6	–	–	–	+++	++	–	++++	++++	+
Control		–	–	–	–	–	–	++++	+++	–

Before antitoxin; lack of protection.

K. M.	7	+	–	–	+++	+++	+	++++	++++	+
Control		–	–	–	–	–	–	++++	+++	–

10,000 units given on sixth day; lack of protection.

K. M.	9	+	–	–	+++	++	+	++++	++++	+
Control		–	–	–	–	–	–	++++	+++	–

10,000 units given on eighth day; lack of protection.

K. M.	17	–	–	–	+	–	–	++++	++++	+++
Control		–	–	–	–	–	–	+++	+++	–

Almost complete protection.

K. M.	36	–	–	–	+	–	–	++++	+++	–
Control		–	–	–	+	–	–	++++	+++	–

No lack of protection.

Table III. This patient did not develop paralysis and was completely cured. Delay in treatment in this case (sixth day) would account for prolonged period of lack of protection.

Case 4. D. H., aged $6\frac{4}{12}$ years. Admitted on sixth day of illness. Exudate + +. This was a case of haemorrhagic diphtheria with epistaxis and haemorrhages into skin.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
D. H.	7	+	–	–	++++	+	–	++++	++++	+
Control		–	–	–	–	–	–	+++	+	–

Table IV. 10,000 units of antitoxin were given on admission. Patient died one day after admission, i.e. on the seventh day of illness with cardiac paralysis. The blood was examined after death, having been taken from the heart. The serum showed marked lack of protection.

Case 5. J. B., aged $7\frac{11}{12}$ years. Admitted second day of illness. Exudate + + +, very toxic.

J. B.	2	–	–	–	++	+	–	++++	+++	–
Control		–	–	–	–	–	–	++	–	–

Before antitoxin; lack of protection

J. B.	9 Post-mortem	–	–	–	+++	++	+	++++	++++	+
Control		–	–	–	–	–	–	++	–	–

60,000 units of antitoxin given (second to fourth day).

Table V. This patient died on the ninth day saturated with toxin. The serum showed a marked lack of protective power.

Case 6. M. B., aged $5\frac{7}{12}$ years. Admitted on fifth day of illness. Exudate + +.

M. B.	5	+	–	–	++++	++	–	++++	++++	+
Control		–	–	–	–	–	–	++++	++	–

Before antitoxin ; lack of protection.

M. B.	7	+	–	–	++	++	–	++++	++++	–
Control		–	–	–	–	–	–	++++	+++	–

30,000 units given fifth to seventh days ; slight lack of protection.

M. B.	21	+	–	–	+	–	–	++++	+++	–
Control		+	–	–	+	–	–	++++	+++	–

No lack of protection.

Table VI. This patient did not develop paralysis and was discharged cured. The serum at the end of twenty-one days showed protection to the haemolysin equal to the control.

Case 7. N. K., aged $4\frac{1}{2}$ years. Admitted on third day. Exudate + +.

N. K.	3	–	–	–	++++	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–

Before antitoxin; lack of protection.

N. K.	7 post-mortem	–	–	–	++	–	–	++++	++++	–
Control		–	–	–	–	–	–	++	–	–

60,000 units antitoxin given on third day ; lack of protection.

Table VII. Patient developed cardiac paralysis on seventh day and died. Serum taken post-mortem showed lack of protection.

Case 8. H. B., aged $15\frac{1}{2}$ years. Admitted fourth day. Exudate + + +.

H. B.	4	–	–	–	+	–	–	+++	++	–
Control		–	–	–	–	–	–	++	+	–

Before antitoxin; slight lack of protection.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
H. B.	7	–	–	–	++++	+++	–	++++	++++	–
Control		–	–	–	–	–	–	++++	+++	–

60,000 units of antitoxin given on fourth day ; lack of protection.

H. B.	15	–	–	–	–	–	–	+++	+	–
Control		–	–	–	–	–	–	+++	++	–

20,000 units given on seventh day ; no lack of protection.

H. B.	26	–	–	–	–	–	–	+++	++	–
Control		–	–	–	–	–	–	+++	++	–

No lack of protection.

H. B.	52	–	–	–	++	+	–	++++	++++	–
Control		–	–	–	++	+	–	++++	++++	–

No lack of protection.

Table VIII. This patient, in spite of a very extensive throat lesion, did not develop paralysis. Large doses of antitoxin were given, and the fact that after these doses the serum showed distinct protection is probably associated with the absence of paralysis.

Case 9. E. R., aged $9\frac{9}{12}$ years. Admitted fourth day of illness. Exudate +.

E. R.	4	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++	+	–

Before antitoxin ; slight lack of protection.

E. R.	11	–	–	–	++++	++	–	++++	++++	++++
Control		–	–	–	–	–	–	++++	++++	+

30,000 units given on fourth to sixth day ; lack of protection.

E. R.	20	–	–	–	++	–	–	++++	++++	++++
Control		–	–	–	++++	–	–	++++	++++	++++

No lack of protection. Ocular paralysis.

E. R.	26	–	–	–	++	–	–	++++	–	–
Control		–	–	–	++	–	–	++++	–	–

No lack of protection.

E. R.	27	–	–	–	++++	+	–	++++	++++	–
Control		–	–	–	++++	–	–	++++	++++	–

No lack of protection.

E. R.	42	–	–	–	++++	+	–	++++	++++	+
Control		–	–	–	++++	–	–	++++	++++	–

No lack of protection. Paralysis of lower limbs.

Table IX. This patient, in spite of a moderate lesion of the throat, developed palate paralysis on the nineteenth day, while the serum showed complete protection on this day. The paralysis became progressively worse and was followed by ocular paralysis and paralysis of the lower limbs. In spite of the progressive paralysis, protection remained constant. The patient recovered slowly and paralysis disappeared by the end of the eleventh week. This case is interesting in that we presume that the toxin entering the blood is responsible for the destruction of serum proteins or other elements of the serum which inhibit the action of haemolysins. On this basis, although on the nineteenth day the blood is free from toxin, paralysis has occurred and progressed, and it must be assumed that the toxin forms very early combination with the nervous system, and one so combined is unaffected by antitoxin.

Case 10. J. L., aged $6\frac{8}{12}$ years. Admitted on the fourth day of illness. Exudate + + +.

J. L.	4	–	–	–	++	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–

Before antitoxin ; slight lack of protection.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
J. L.	8	–	–	–	++++	++++	–	++++	++++	++
Control		–	–	–	++++	++++	–	++++	++++	++
80,000 units on fourth to seventh day ; no lack of protection. Palate paralysis.										
J. L.	9	–	–	–	++++	–	–	++++	++	–
Control		–	–	–	++++	–	–	++++	++	–
No lack of protection.										
J. L.	15	–	–	–	++	+	–	++++	++	–
Control		–	–	–	–	–	–	++	+	–
Lack of protection. Ocular paralysis.										
J. L.	16	–	–	–	++	+	–	+++	+	–
Control		–	–	–	–	–	–	+	–	–
Lack of protection. Paresis of lower limbs.										
J. L.	22	++	+	–	+++	++	–	++++	++++	–
Control		–	–	–	+++	–	–	++++	++++	–
Lack of protection.										
J. L.	33	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
No lack of protection. Pharyngeal paralysis.										
J. L.	43	–	–	–	–	–	–	++++	++++	+
Control		–	–	–	–	–	–	++++	++++	–
No lack of protection.										
J. L.	50	–	–	–	+	–	–	++++	+	–
Control		–	–	–	–	–	–	++++	+	–
No lack of protection. General paralyses disappearing.										

Table X. This patient showed slight lack of protection before injection of antitoxin ; after 80,000 units, the blood test showed complete protection, yet at the same time the patient developed palate paralysis on the eighth day (precocious paralysis) which became progressively worse and was followed by ocular paralysis, paralysis of lower limbs with loss of knee-jerks, and finally paralysis of pharyngeal muscles. The protection shown on the eighth day was only temporary, and was probably due to the neutralizing action of the large amount of antitoxin which was injected. More toxin, however, must have been produced, for lack of protection was again shown on the fifteenth day, and remained until the thirty-third day, when complete protection was shown and remained. The paralysis gradually improved after the fifteenth day.

Case 11. K. B., aged $6\frac{10}{12}$ years. Admitted on the fourth day of illness. Exudate + +.

K. B.	4	++++	+	–	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	++++	–	++++	++++	++++
Before antitoxin ; marked lack of protection.										
K. B.	8	++++	++	+	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	–	–	++++	++++	+++
60,000 units on fourth to seventh day ; marked lack of protection.										
K. B.	12	+	–	–	+	–	–	++++	++++	++++
Control		–	–	–	–	–	–	+	–	–
Marked lack of protection.										
K. B.	19	++	+	–	++++	+++	–	++++	++++	+
Control		–	–	–	–	–	–	++++	+++	+
Palate paralysis. Marked lack of protection.										
K. B.	25	+	+	–	++++	+	–	++++	++++	+
Control		–	–	–	–	–	–	++++	++	+
Lack of protection.										

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
K. B.	33	++++	+++	–	++++	++	–	++++	++++	+
Control		–	–	–	–	–	–	++++	++++	+
		Ext. ocular paralysis. Lack of protection.								
K. B.	40	–	–	–	++	–	–	++++	++	–
Control		–	–	–	–	–	–	+++	++	–
		Slight lack of protection.								
K. B.	41	–	–	–	+	–	–	++++	++	–
Control		–	–	–	–	–	–	++++	++	–
		Slight lack of protection.								
K. B.	47	–	–	–	+	–	–	++++	++	–
Control		–	–	–	–	–	–	++++	++	–
		Almost normal protection.								
K. B.	52	–	–	–	–	–	–	+++	++	–
Control		–	–	–	–	–	–	+++	++	–
		Normal protection.								
K. B.	65	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
		Normal protection.								

Table XI. This patient showed lack of protection in varying degree up to the fifty-second day of illness. This finding may be accounted for by either the continuance of toxin formation and the inability of the body to neutralize it either by natural antitoxin formed or antitoxin inoculated, or inability of the body as a result of a secondary anaemia to restore to the serum the constituents destroyed by the toxin. After the forty-first day there was a gradual diminution in lack of protection, yet the paralysis continued progressive. Protection became normal on the fifty-second day and the paralyses gradually recovered.

Case 12. M. A. G., aged $13\frac{1}{2}$ years. Admitted on fourth day of illness. Exudate + + +.

M. A. G.	4	+++	+	–	++++	++++	+++	++++	++++	++++
Control		+	–	–	++	++	–	++	++	–
		Before antitoxin; lack of protection.								
M. A. G.	6	–	–	–	++	–	–	++++	–	–
Control		–	–	–	–	–	–	+	–	–
		60,000 units on fourth to sixth day; lack of protection.								
M. A. G.	19	++++	++++	++++	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	–	–	++++	++++	–
		Palate paralysis. Lack of protection.								
M. A. G.	27	++++	++	–	++++	+	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
		Lack of protection.								
M. A. G.	34	–	–	–	–	–	–	++++	–	–
Control		–	–	–	–	–	–	++++	–	–
		Normal protection.								
M. A. G.	35	–	–	–	++	–	–	++++	++++	–
Control		–	–	–	++	–	–	++++	++++	–
		Normal protection. Ocular paralysis.								
M. A. G.	41	–	–	–	–	–	–	++++	++++	+
Control		–	–	–	–	–	–	++++	++	+
		Normal protection. Paralyses improved.								

Table XII. This patient showed lack of protection until the thirty-fourth day. Palate paralysis occurred during this period and was progressive. Ocular

paralysis occurred during the period of normal protection. Both paralyses disappeared after the fiftieth day.

Case 13. J. B., aged 6 years. Admitted fourth day of illness. Exudate + +.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
J. B.	4	–	–	–	++++	–	–	++++	++++	++++
Control		–	–	–	–	–	–	++++	++++	–
Before antitoxin ; lack of protection.										
J. B.	13	–	–	–	+	–	–	++++	++++	++++
Control		–	–	–	–	–	–	++++	++++	+
40,000 units given fourth to sixth day ; normal protection.										
J. B.	30	–	–	–	–	–	–	++++	–	–
Control		–	–	–	–	–	–	++++	+	–
Normal protection.										

Table XIII. This patient's serum showed normal protection on the thirteenth day after 40,000 units of antitoxin. Protection remained normal. This patient did not develop paralysis and was discharged cured.

Case 14. H. B., aged 6 years. Admitted on second day of illness. Exudate + +, increasing to + + + on third day.

H. B.	3	–	–	–	+	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
After 10,000 units ; normal protection.										
H. B.	6	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
After 60,000 units ; normal protection.										
H. B.	11	–	–	–	+	–	–	++++	+	–
Control		–	–	–	++	–	–	++++	++++	–
Palate paralysis. Normal protection.										
H. B.	18	–	–	–	+	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
Ocular paralysis. Normal protection.										
H. B.	27	–	–	–	++++	–	–	++++	–	–
Control		–	–	–	++++	+	–	++++	–	–
Normal protection.										

Table XIV. This patient was given antitoxin as early as the second day, and this will account for the complete protection which the serum showed from an early stage of the disease. In spite of the complete protection the nervous system was affected, as shown by the appearance of palate paralysis on the eleventh day, and ocular paralysis on the eighteenth day.

Case 15. T. B., aged 13 years. Admitted on the fourth day of illness. Exudate + +.

T. B.	5	+	–	–	++++	+	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–
After 20,000 units antitoxin ; lack of protection.										
T. B.	9	–	–	–	–	–	–	++++	+	–
Control		–	–	–	–	–	–	++++	–	–
Another 10,000 units on sixth day. Normal protection.										
T. B.	26	–	–	–	+++	+	–	+++	–	–
Control		–	–	–	+++	+	–	+++	–	–
Normal protection.										

Table XV. This patient did not develop paralysis and got quite well.

Case 16. J. P. M., aged $9\frac{11}{12}$ years. Admitted on fourth day of illness. Exudate + +.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
J. P. M.	4	–	–	–	++	+	–	++++	++++	++
Control		–	–	–	+	–	–	++++	+++	–

Before antitoxin; slight lack of protection.

J. P. M.	18	–	–	–	++++	++++	+	++++	++++	++++
Control		–	–	–	++++	++++	–	++++	++++	++++

Between fourth and sixth day, 35,000 units were given. Normal protection.

J. P. M.	25	–	–	–	+	–	–	++++	+	–
Control		–	–	–	–	–	–	++	–	–

Anaemia; slight lack of protection.

J. P. M.	26	–	–	–	++++	–	–	++++	+++	–
Control		–	–	–	++	–	–	++++	–	–

Anaemia; slight lack of protection. Some paralysis of lower limbs on thirty-fifth day.

J. P. M.	43	–	–	–	–	–	–	++++	++++	+
Control		–	–	–	–	–	–	++++	++++	–

Normal protection.

Table XVI. Complete protection appeared in this case by the eighteenth day after 35,000 units of antitoxin. The slight lack which was shown again on the twenty-fifth day and remained till about the forty-third day was probably associated with the post-diphtheritic anaemia which occurred. Some incomplete paralysis of the lower limbs was evident on the thirty-fifth day, but this recovered after a fortnight. No further paralysis developed.

Case 17. B. C., aged 7 years. Admitted on fifth day of illness. Exudate + +.

B. C.	46	–	–	–	++++	+	–	++++	++++	–
Control		–	–	–	+	–	–	++++	+++	–

Palate paralysis on forty-third day; slight lack of protection.

B. C.	53	++++	++	–	++++	++++	++	++++	++++	++++
Control		–	–	–	++++	++++	–	++++	++++	++++

Ocular paralysis, forty-ninth day; slight lack of protection.

B. C.	58	++	+	–	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	++++	–	++++	++++	++++

Partial paralysis of lower limbs. Slight lack of protection.

B C.	64	–	–	–	–	–	–	++++	–	–
Control		–	–	–	–	–	–	+	–	–

Slight lack of protection.

B. C.	72	+	–	–	++++	–	–	++++	++++	+
Control		–	–	–	–	–	–	++++	+++	+

Slight lack of protection.

Table XVII. This patient received 30,000 units of antitoxin from the fifth to the seventh day, but tests of the serum were not made until the forty-sixth day, i.e. three days after the first appearance of paralysis. Some lack of protection existed up to the seventy-second day. During this period a series of paralyses developed which gradually recovered by the seventy-second day in spite of the still existing lack of protection of the serum.

Case 18. A. L., aged 14 years. Admitted fourth day of illness. Exudate +, fauces and also laryngeal.

A. L.	4	–	–	–	+	–	–	++++	+++	–
Control		–	–	–	+	–	–	++++	+++	–

Before antitoxin; normal protection.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
A. L.	14	–	–	–	++	–	–	++++	+	–
Control		–	–	–	+	–	–	++	–	–

Lack of protection. 30,000 units of antitoxin from fourth to sixth day.

A. L.	21	++++	+	–	++++	++	–	++++	++++	++++
Control		–	–	–	+++	+	–	++++	++++	+

Lack of protection.

A. L.	28	+	–	–	++++	++++	+	++++	++++	++++
Control		–	–	–	–	–	–	++++	++++	+

Slight palate paralysis. Lack of protection.

A. L.	35	++++	+	–	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	++++	–	++++	++++	++++

Incomplete paralysis of lower limbs. Lack of protection.

A. L.	42	–	–	–	++++	–	–	++++	++++	–
Control		–	–	–	–	–	–	+	–	–

Lack of protection.

A. L.	45	++++	++++	+++	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	++++	++++	++++	++++	++++

Lack of protection.

Table XVIII. This patient showed lack of protection during the whole period in hospital. There was only slight palate paralysis on the twenty-first day, and incomplete paralysis of the lower limbs on the thirty-fifth day, which very quickly recovered. The continued lack of protection was probably associated with post-diphtheritic anaemia which was very marked.

Case 19. F. B., aged 9 years. Admitted on seventh day of illness. Exudate +.

F. B.	7	–	–	–	+++	+	–	++++	++++	++
Control		–	–	–	+++	+	–	++++	++++	+

Before antitoxin; no lack of protection.

F. B.	16	–	–	–	++++	++	–	++++	++++	++++
Control		–	–	–	++++	+	–	++++	++++	++++

10,000 units given on seventh day; no lack of protection.

F. B.	30	–	–	–	++++	++++	++++	++++	++++	++++
Control		–	–	–	++++	++++	++++	++++	++++	++++

No lack of protection.

Table XIX. This patient's serum showed no lack of protection during the whole period of illness and did not develop paralysis.

Case 20. E. T., aged $6\frac{4}{12}$ years. Admitted on third day of illness. Exudate +.

E. T.	3	++++	+++	–	++++	++++	++++	++++	++++	++++
Control		++++	–	–	++++	++++	++	++++	++++	++++

Before antitoxin; slight lack of protection.

E. T.	29	++++	–	–	++++	++	+	++++	++++	++++
Control		–	–	–	–	–	–	++++	++++	–

After 30,000 units (third to fifth day); lack of protection. Some paralysis of lower limbs (thirtieth day).

E. T.	36	–	–	–	+	–	–	++++	–	–
Control		–	–	–	+	–	–	++++	–	–

Normal protection.

Table XX. This patient's serum showed lack of protection in spite of early antitoxin treatment. There was lack of protection as late as the twenty-ninth day, but serum showed normal protection again on the thirty-sixth day. Some paralysis of the lower limbs occurred on the thirtieth day, which disappeared by the fortieth day.

Case 21. L. M. E., aged 14½ years. Admitted on seventh day of illness. Exudate + +.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
L. M. E.	57	–	–	–	++	+	–	++++	+	–
Control		–	–	–	–	–	–	++	–	–

60,000 units previously injected (seventh to tenth day); lack of protection.

L. M. E.	80	–	–	–	+	–	–	+++	+	–
Control		–	–	–	–	–	–	+++	+	–

Normal protection.

Table XXI. This was a case in which treatment was delayed till the seventh day of illness. Palate paralysis developed on the sixteenth day, cardiac paralysis on the forty-second day, and paralysis of the lower limbs on the seventieth day. The patient's serum showed lack of protection as late as the fifty-seventh day, and had recovered its protective power by the eightieth day, by which time the paralyses had gradually recovered.

Case 22. K. M. Y., aged 12 years. Admitted on second day of illness. Exudate + +.

K. M. Y.	2	–	–	–	–	–	–	++	++	–
Control		–	–	–	–	–	–	++	++	–

Before antitoxin; normal protection.

K. M. Y.	8	–	–	–	–	–	–	++++	+	–
Control		–	–	–	–	–	–	++	–	–

After 20,000 units on second to fourth day; slight lack of protection.

K. M. Y.	15	–	–	–	++++	+	–	++++	++++	+
Control		–	–	–	++++	+	–	++++	++++	+

Normal protection.

K. M. Y.	24	–	–	–	++++	–	–	++++	++++	++++
Control		–	–	–	++++	–	–	++++	++++	++++

Normal protection.

Table XXII. This patient's serum showed early protection, i. e. by the fifteenth day, and no paralyses developed.

Case 23. J. L., aged 5 years. Admitted on sixth day of illness. Exudate + +.

J. L.	39	–	–	–	++	–	–	++++	+++	++
Control		–	–	–	–	–	–	++	–	–

After 35,000 units antitoxin (sixth to eighth day); lack of protection.

J. L.	67	–	–	–	+	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	+++	–

Almost complete protection.

Table XXIII. Treatment in this case was delayed till the sixth day, and serum showed lack of protection as late as the thirty-ninth day. Paralysis was progressive, ocular paralysis first appearing on the thirteenth day, palate paralysis on the sixteenth day, and cardiac paralysis on the thirty-third day, which all gradually recovered. Paralysis of the lower limbs commenced on the seventieth day, three days after the serum had shown almost complete protection.

Case 24. L. W., aged 7 years. Admitted on second day of illness. Exudate + +, very toxic case.

L. W.	40	–	–	–	+++	+	–	++++	++++	–
Control		–	–	–	–	–	–	++++	+	–

Lack of protection.

	Day of Illness.	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
L. W.	52	–	–	–	+	–	–	++++	++	–
Control		–	–	–	–	–	–	+++	+	–

Slight lack of protection.

Table XXIV. 45,000 units of antitoxin given from second to fourth day. Palate paralysis developed on the sixth day (precocious paralysis). On the fifty-second day some paralysis of lower limbs developed, which gradually improved. The serum of this patient showed lack of protection for a long period.

Case 25. E. L., aged $6\frac{10}{12}$ years. Admitted on sixth day of illness. Exudate + +.

E. L.	12	++++	–	–	++++	++++	++	++++	++++	++++
Control		–	–	–	++++	++++	–	++++	++++	–

After 20,000 units (sixth to seventh day); lack of protection.

E. L.	14	–	–	–	+++	++	+	++++	++	–
Control		–	–	–	++	++	–	++	++	–

Slight lack of protection.

E. L.	25	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–

Normal protection.

E. L.	33	–	–	–	+	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–

Normal protection.

E. L.	41	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–

Normal protection.

E. L.	48	–	–	–	–	–	–	++++	++++	–
Control		–	–	–	–	–	–	++++	++++	–

Normal protection.

Table XXV. This patient developed palate paralysis on the ninth day after 20,000 units of antitoxin. She also developed some cardiac paralysis, which disappeared by the eleventh day. The palate paralysis got steadily worse and paralysis of lower limbs appeared on the forty-first day. The paralyses were gradually improving on the forty-eighth day, and the patient ultimately got quite well.

Discussion.

The results given above show quite definitely that in diphtheria the toxin acts on the serum in such a way that the protective capacity of the latter against a haemolysin such as sodium ricinoleate is markedly impaired. From the work of Ponder, working with saponin as the haemolysin, it seems probable that the proteins are the portions of the serum attacked. This impairment of its protective capacity occurs early in the disease, and if the case is treated early and adequately with antitoxin and is uncomplicated, this protective capacity is in most cases restored by the beginning of the third week.

It appears, therefore, that this action on the serum in diphtheria might be made use of in assessing the toxicity of a case for the purpose of graduating the dose of antitoxin to be given and for prognostic purposes.

Our cases can roughly be divided into four groups.

I. Uncomplicated cases with serum showing normal protection against haemolysin by the third week.

II. Cases which show lack of protection by the serum occurring concurrently with a series of paralyses, both lack of protection and paralysis lasting several weeks.

III. Cases showing early complete protection, yet developing paralyses concurrently with complete protection by the serum.

IV. Cases of early hypertoxaemia and death, showing marked lack of protection by the serum.

Group I. (Cases 1, 2, 3, 6, 8, 13, 15, 19, and 22.) In Group I cases there was a steady neutralization of the toxin by antitoxin as judged by the clinical condition of the patients, and a progressive gradient to the normal of the protective power of the serum against haemolysin. There was no fixation of the toxin by the nervous system as shown by the absence of paralysis, and the appearance of a normal protective state of the serum would indicate an absence or complete neutralization of the toxin circulating in the blood. This occurred in most of this group of cases about the third week.

Group II. (Cases 11, 12, 16, 17, 18, 20, 21, 23, and 24.) In this group paralyses occurred and progressed, and the lack of protection was demonstrated in the systemic circulation for lengthy periods varying from forty-three to eighty days. The cases showed great irregularity in the time of onset of paralysis, in one case as early as the sixth day and in another as late as the forty-third day. Antitoxin treatment did not appear to modify the onset of paralysis in any way. As the serum showed lack of protection throughout, it would indicate that complete neutralization of toxin had not occurred and that some of this toxin had gone into combination with the nervous system.

Group III. (Cases 9, 10, 14, and 25.) This group of cases, though small, is very important, in that it illustrates the independent onset of paralysis after the serum has shown complete protection and therefore neutralization of the toxin. Ehrlich's 'toxone' might explain this phenomenon, where the toxin, although neutralized, still has some portion of it capable of combining with the nervous system and causing paralysis. Another point of view is that some of the toxin may have combined with the nervous system before antitoxin was given and thus already combined could not be neutralized by any subsequent antitoxin.

Group IV. (Cases 4, 5, and 7.) This was a group of fatal cases, and all died of early cardiac failure in spite of antitoxin treatment, and showing in two of them marked lack of protective power of the serum.

Conclusions.

In diphtheria the protective power of the serum against a haemolysin is markedly diminished, this protective power returning in simple uncomplicated cases by the end of the third week. In most cases of paralysis this diminished protective power lasts for a considerable time. In a few cases of paralysis there

will be no interference with the protective power of the serum. In fatal cases there is a marked loss of this protective power.

This protection of the serum against haemolysin should be estimated early in the disease as an indication of the amount of toxin present in the blood, in order to give some index to the amount of antitoxin to be injected, and at various periods of the disease in order to assess the prognosis and the possible development of paralysis.

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STUDIES OF AN INSULIN-RESISTANT DIABETIC[1]

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MANY cases of diabetics who have not reacted normally to insulin have been reported, and have been termed 'insulin resistant' or 'refractory' to insulin. When these reports are closely studied, it would appear that, with the possible exception of cases moribund in coma, no well-authenticated case is on record in which insulin in large doses has had no effect in lowering the blood-sugar of the patient. Such refractory cases are therefore only relatively and not absolutely insulin resistant. The conditions which tend to make a diabetic insulin resistant are well known, and have been discussed by the author and others (1 and 2). Most of the numerous cases published can be accounted for by the following factors which antagonize insulin action: (1) Concurrent infections and sepsis. (2) Over-activity of the thyroid, pituitary, and (?) suprarenal glands, physiological antagonists to insulin. (3) Inefficient treatment of severe cases with high or imperfectly controlled diets and insufficient insulin. (4) Liver disease (3), especially cirrhosis and bronzed diabetes, has been suggested, but when these cases are studied critically there seems no reason for not including them in the third category.

The case reported in this paper falls into none of these categories, as far as can be ascertained. It has been possible, apparently for the first time, to study the reaction to insulin in great detail and to determine where it fails and the probable defect in the patient's metabolism.

History of the Case.

A synopsis of the history of the case is given in Table I, and I am greatly indebted to Dr. Jacob of Nottingham for the earlier records. S. J., a boy of 17, developed diabetes fairly acutely in March 1925 without any preceding illness to account for it. He was admitted to Nottingham General Hospital on April 14, 1925, with severe acidosis. After a month's treatment his condition was easily controlled by a diet of 36 C., 38 P., and 83 grm. fat and 20 units of insulin b.d. His reaction to insulin was normal, for the blood-sugar fell from a fasting level of 0·166 per cent. to 0·110 per cent. 3 hours after 20 units and breakfast. He became worse in January 1926 and required more insulin, but again his blood-sugar fell after insulin and breakfast in the usual way. By the end of 1926 he was given 120 units a day on the same diet rigidly maintained, and even this did not control his glycosuria and ketosis. In October he became precomatose and

[1] Received December 10, 1927.

was only rescued by enormous doses of insulin. After this his diet was raised to prevent any temptation to his breaking it, and 250 units a day did not quite abolish his glycosuria. It was obvious that he was an unusual case, and Dr. Jacob was kind enough to send him to me for further investigation.

On admission to King's College Hospital on January 13, 1927, he was at first kept on the same diet and 220 units of insulin a day, and was found to excrete 55 grm. of sugar, an insulin glucose equivalent of 2 units to 1 grm. of sugar (see Table II). When 55 grm. of carbohydrate were cut out of the diet he became practically sugar free. His blood-sugar picture at that time is shown in Table III, and will be discussed in more detail later. The obvious unusual feature was that his fasting blood-sugar was low, and that it rose after food in spite of large doses of insulin. One day he was given 400 units, and even this failed to stop the rise of blood-sugar after food, although it was reduced to normal late in the evening. As the effect of insulin was obviously much less than normal, the effect of omitting it altogether was observed. He at once relapsed into the full diabetic condition and at the end of five days was precomatose and excreted 140 grm. of sugar and much ketone bodies. He showed all the usual diabetic changes. The urine nitrogen changed from a positive balance of 1 grm. to a negative of 5–7 grm.; the blood cholesterol rose from 213 to 345 mg. per 100 c.c.; the alveolar CO_2 fell from 4·9 to 2·8 per cent. Clinically slight air hunger and vomiting were commencing.

He was easily rescued by insulin, and after this it was found that far less insulin, 80 units a day, controlled his condition. An attempt was made to substitute synthalin, partially and entirely, for the insulin, but again he became precomatose in precisely the same time, although his sugar excretion reached only 77 instead of 140 grm. After this the diabetes was again fully controlled by 80 units a day and he was discharged from hospital. He kept rigidly to his diet (of this there is no doubt), but the glycosuria returned a little and the blood-sugar rose on one occasion to 0·331 per cent. Insulin was gradually increased to 160 units a day. He was again admitted to King's College Hospital for some further investigations which are detailed later.

General condition. There is no history of diabetes in the family. The patient had 'convulsions' and measles in childhood, but no serious illnesses and no illness immediately before the onset of the diabetes.

He was thin, 20 lb. under weight for his size and age, with poor musculature, not robust—very different indeed from the usual juvenile diabetic adequately treated with diet and insulin. In keeping with this was the absence of ankle-jerks. The knee-jerks were just present on reinforcement. He had no neuritis nor any other abnormality in his nervous system. The Wassermann reaction was negative. His sexual function was normal. Diastase tests were normal and the van den Bergh reaction. The external pancreatic secretion seemed normal from the examination of the faeces and the kidney and liver function tests satisfactory. The liver was not palpable. The closest search revealed no septic focus anywhere, nor was there any evidence that the functions of the thyroid, the pituitary, or the suprarenal were abnormal. He suffered from slight and intermittent acne rosacea which had been present for years. The only abnormal feature in his general condition was the presence of a high degree of *eosinophilia*, estimations from January to September 1927 showing percentages of 12, 20, 11, 15, 17·5, and 17·5 at various times. The total white cell count had been low, 4,000 to 6,000 per cm., and slight secondary anaemia was present. Such a degree of eosinophilia is more than can be produced by slight acne rosacea, and a parasitic condition was suspected. Repeated examination of the faeces has never shown ova or parasites. It has since been discovered that many insulin-treated diabetics have an abnormally high eosinophilia, though not so high as this case. The highest other observed so far is 12 per cent., but 6 per cent. is quite common.

There was therefore no obvious reason why this patient required far more insulin than the ordinary severe diabetic. Insulin certainly had an effect on him and kept him out of coma, and when enormous doses are given the blood-sugar can be reduced to the normal level. His *quantitative* reaction to insulin was therefore very slight, and we shall see that his *qualitative* reaction was different from the ordinary diabetic's.

Blood-sugar Studies of the Case and their Significance.

A series of observations are recorded in Tables III to VI which were carried out to determine the exact point of failure of insulin action in this case. For purposes of comparison, some records are given of the insulin reactions of a 'normal' severe diabetic (R. D. L.) under similar conditions. These latter reactions will be familiar to all who treat and study diabetics closely. The results are grouped under various headings showing special features, and their significance is discussed separately in the light of what is already known of the details of insulin action. The most widely accepted view is that insulin has a double action: (1) that it converts glucose circulating in the blood into a store of glycogen in the liver and muscles, and (2) that it checks glycogenolysis and the formation of new sugar (and ketones at the same time) from protein and perhaps from fat. These are the two manifestations of insulin action, but it would seem unlikely that such a substance as insulin would carry out more than one step in carbohydrate metabolism. Its second action, therefore, in checking neoglucogenesis is probably dependent on its first in supplying available carbohydrate (glycogen), which removes the stimulus to the endogenous production ol new sugar. The observations about to be recorded are discussed in the light of these two actions of insulin.

I. *Low fasting blood-sugar and rise after food in spite of insulin.* This feature became obvious as soon as detailed blood-sugar examinations were made. It is seen in Table III, where the fasting blood-sugar is comparatively low and rises after the carbohydrate of the breakfast (20 grm.) in spite of large doses of insulin. This occurred regularly every day, even on 24.1.27, in spite of 100 units of insulin. However, as the result of giving 400 units of insulin on that day, the blood-sugar had fallen to normal in the evening. In Table IV a comparison is given of the effect of the breakfast carbohydrate on the blood-sugar with and without 40 units of insulin. Unfortunately the fasting blood-sugar levels are not very close together (this is commonly found in severe diabetics), but it is obvious that on 15 and 16.3.27 the type of the curve and indeed the absolute rise in the blood-sugars are practically identical with and without insulin. The effect of 80 units some months later, on 25.8.27, was to check the rise to some extent as compared to next day.

For comparison, the usual type of curve in a severe diabetic is given in Table III (R. D. L.) and shows the exact reverse. The fasting blood-sugar is the highest of the day, rapidly falls under the effect of insulin to normal in about four hours, and rises again as the insulin action wears off. The explanation of

this is taken to be that the insulin changes the circulating glucose into stored glycogen in the liver and muscles, and that, when the action of insulin is over, the glycogen from the liver reappears as glucose in the blood. It is almost certain that the glycogen of the muscles remains there as such until used, and does not reappear in the blood as glucose (4, 5, and 6).

It is obvious that in the above case insulin cannot deal with ingested carbohydrate in the usual way, and it is most probable that it fails to form glycogen. But the fact that the blood-sugar tends to fall to normal, or certainly lower levels, as the day goes on and after succeeding doses of insulin, might suggest that the action of insulin may only be delayed in this case, due to slow absorption or a slow physiological response. The experiments in the next section show that this is not the complete explanation.

II. *Effect of insulin on the fasting blood-sugar.* Table V shows that these large doses of insulin have a very definite effect in lowering the fasting blood-sugar. The time at which the fall commences is not delayed as compared with other diabetics. But the total fall in blood-sugar is less than normal; for ordinary diabetics, and indeed normal individuals, would usually reach a very severe degree of hypoglycaemia with 40 units of insulin unbalanced with food. The effect of 10 units is definitely delayed. Given intravenously, insulin was not appreciably quicker in action, but did produce a lower degree of hypoglycaemia than subcutaneously. In none of these experiments was it necessary to give glucose to counteract the slight symptoms of hypoglycaemia that did occur. These experiments show that the failure of this patient to deal with ingested carbohydrate is not due to the poor absorption or delayed action of the insulin, and that some other explanation must be sought.

It is quite possible that the fall in blood-sugar recorded in Table V is due almost entirely to the second action of insulin in checking the new production of sugar and so allowing the blood-sugar concentration to fall as it is used up. This is almost certainly the chief action of insulin in small normal animals. Indeed it has never been shown that the first action of insulin, the change of glucose into glycogen, takes place at low blood-sugar levels. Therefore it is possible that the above fall in blood-sugar is due entirely to the second action of insulin and not to any glycogen formation.

The experiment with ergotamine (see Table V) lends certain support to this hypothesis. This drug paralyses the output of sugar from the liver by its action on the sympathetic and causes a gradual fall in blood-sugar. Even in animals it requires almost lethal doses to cause a considerable fall in blood-sugar, and it is not possible to give really effective doses to man without too great upset. But in the period of its maximum action, as shown by the simultaneous slowing of the pulse-rate, the drop in the blood-sugar between three-quarters and one and a half hours is nearly as great as after insulin. The blood-sugar did not fall any farther, but the effect of the ergotamine had nearly worn off by then and it was not deemed wise to give more. The effect of insulin and ergotamine in this patient was very comparable, and, as we know that the fall in blood-sugar from

the latter is due to the prevention of new sugar entering the blood-stream from the liver, it seems justifiable to suggest that this is the main action of insulin in these experiments.

We have, therefore, presumptive evidence that insulin fails to store away ingested carbohydrate normally in this case, but can lower the blood-sugar by inhibiting neoglucogenesis. We shall now produce evidence of another kind to show that carbohydrate is not normally stored or only to a very slight extent.

III. *A prolonged comparison between this case and an ordinary diabetic.* Table VI shows a more prolonged comparison of the effect of insulin and food between S. J. and a 'normal' severe diabetic, R. D. L. The experiment was started at 6 p.m., when neither had had insulin for 10 hours, and was continued long enough to follow the course of the blood-sugar when the insulin action had quite worn off. Both had the same supper containing 20 grm. C., 25 P., and 40 F., and the respective doses of 80 and 20 units of insulin. R. D. L., as usual with a severe diabetic who has had no insulin for many hours, started at a high blood-sugar level. This fell rapidly, reached normal in four hours, and remained at the same level for ten hours, perhaps longer, but had risen very rapidly by fourteen hours to the high figure of 0·321 per cent. This is a surprisingly rapid rise and was higher than his usual fasting level. The experiment was carried no farther because the timing of the rise in blood-sugar had been fairly closely observed. This phenomenon is the rule in severe diabetes, but what was unexpected was the constancy of the blood-sugar from the fourth to the tenth hour. It is well known that the maximum hypoglycaemic effect of insulin occurs about the fourth hour, but the prolonged depression of the blood-sugar and the sudden and steep rise after the tenth hour were unexpected. It may be that the time of duration of the two actions of insulin is different, the glycogen-forming action taking place for the first few hours, but the check on glycogenolysis and the new formation of sugar lasting much longer. The sudden elevation of the blood-sugar from endogenous sources is no exceptional phenomenon, and I have frequently observed patients whose blood-sugar was about 0·08 per cent. late in the evening have fasting blood-sugars next morning of over 0·3 per cent. This sudden rise of blood-sugar is almost certain to come from a release of glycogen from the liver (cf. the effect of adrenalin), and not from neoglycogenesis from protein or fat, which one would imagine to be a much slower process. From recent work (6) it appears that such a rapid replenishment of blood-sugar cannot take place to any great extent, if at all, from muscle glycogen.

S. J., on the other hand, showed an entirely different blood-sugar picture. He started at a low level, showed the usual, but only slight, rise after food, in spite of 80 units of insulin, and reached his lowest point a little later than R. D. L., at the sixth hour. The turn of the tide in his blood-sugar also occurred at, or soon after, the tenth hour, but it was a very low tide compared with R. D. L. At the fourteenth, seventeenth, and nineteenth hours his blood-sugar had risen slightly but definitely, which I think must be taken as evidence of slight glycogenolysis. The fast was continued and the blood-sugar fell *per se* to the

hypoglycaemic level of 0·065 per cent. at the twenty-sixth hour. With the recollection of several cases of fatal hypoglycaemia which have been reported (7 and 8) as occurring in this way, he was given his usual supper in the evening and the blood-sugar rapidly rose again and was still higher next morning. The course of his blood-sugar was a striking contrast to R. D. L.'s, and can be best explained by the assumption that he had formed no glycogen store, or only a minimal amount, in his liver, and that glycogenolysis did not occur when the insulin action had worn over, or only to a very slight extent. This was followed by a spontaneous hypoglycaemia when that small amount of glycogen had been used up.

Other observations. The effect of insulin on the inorganic phosphates of the blood is shown in Table V, and the usual diminution of phosphates after insulin is observed. This is a constant feature of insulin action, and has been suggested as the first stage in its action, the formation of a hexose diphosphate as an intermediate stage on the way to glycogen. Whatever may be the significance of this change in the blood phosphates, it was clearly not the point of failure of insulin action in this case.

The effect of exercise in increasing the hypoglycaemic action of insulin was also investigated, and the results are shown in Table IV. The effect of exercise in other diabetics is always to increase the rapidity and the depth of the fall in blood-sugar to a marked extent (9), but this increase of insulin action was absent in this patient, in spite of two hours' very hard exercise on a fixed bicycle and a rowing machine. This would seem to show a definite defect in the muscular use of sugar through insulin action, and his poor muscularity also suggested an inability to use carbohydrate normally. We know that a glycogen stage is an essential for the use of carbohydrate as fuel in the muscles, and it may be that the glycogenic function of the muscles as well as the liver was defective in this case.

Further Discussion.

A discussion of the significance of the experiments has already been undertaken in the last section, and leads to the conclusion that the defect in insulin action in this case lay not in its poor absorption or delayed action, but in its failure to form glycogen in the usual way. It is doubtful if one can arrive at the reason of this failure, but it is tempting to prolong the discussion a little in considering the possibilities.

An organic defect in the liver or muscles. If some organic tissue-change were present in the liver and muscles, this might account for the failure to store glycogen normally. It is in connexion with the liver that the above experiments show most clearly the failure to store glycogen after insulin and to give up sugar again when insulin is withheld, like an ordinary case of diabetes. Although it is rare for liver disease to affect the glycogenic function to any marked extent, yet this may occur. Wagner and Parnaś (10) have published a

case of a boy with a greatly enlarged liver in whom they describe an extraordinary upset in carbohydrate metabolism. They found that his fasting blood contained practically no sugar, always under 0·02 per cent., but that a high hyperglycaemia was present after food—up to 0·42 per cent. Adrenalin had no hyperglycaemic action. They concluded that the organic structural change in the liver, whose nature remained undetermined, had destroyed the glycogenic function of the liver, so that the blood-sugar rose and fell to extreme limits. There is, however, not the slightest evidence of liver disease in the patient now under discussion.

As regards the muscles, the only evidence pointing to their abnormality was their very poor development and the fact that exercise did not have the usual effect of increasing the hypoglycaemic effect of insulin. The electrical reactions were normal, and there was no sign of the primary degenerations in which disturbance of carbohydrate metabolism has been recorded (11 and 12).

There was therefore no evidence that the liver or muscles are organically abnormal in this case, and yet they both seem to have the same defect in carbohydrate utilization. It would be an extraordinary coincidence if both the muscles and liver were organically abnormal, and it is much more likely that some other factor is lacking which they both require to form glycogen after insulin is administered.

Lack of a coenzyme necessary to insulin action. This would appear to be the most likely defect in this case. It seems quite possible that insulin, in the formation of glycogen from glucose, may perform only one step and that other enzymes or hormones are necessary for the complete process. It has been suggested on considerable evidence that the first step, perhaps the only step, in insulin action is the formation of a hexose diphosphate. If this is so, it cannot be the point of failure in this case, because insulin produces the usual fall in blood-phosphates. But it may be in the next stage from hexose diphosphate → glycogen that the defect occurs.

It is of course possible that some unusual inhibitory substance is present which prevents the normal action of insulin in forming glycogen. Such a substance, or a similar one, has recently been described under the name of 'glykaemin' by Haüsler and Högler (13), but their experiments, although suggestive, require confirmation.

The recovery of carbohydrate tolerance after the omission of insulin. It is not suggested that the ability of this case to form glycogen was altogether lacking, but merely that it was very reduced, indeed strictly limited by some factor other than insulin. When his stores of carbohydrate were filled to their limited extent, increase in the dose of insulin did not increase his use of carbohydrate quantitatively as it does in the usual diabetic. The enormous improvement in his carbohydrate tolerance, and in the efficacy of insulin action after the period of omitting insulin, is worth discussing in this connexion. Table II shows that whereas he excreted some 5 grm. of sugar while on 220 units of insulin before the omission of all insulin for five days, afterwards his condition

was much better controlled by only 80 units on practically the same diet. This is a change in the glucose equivalent of insulin from half a grm. to nearly 1·4 grm. per unit, a very striking change. This could not be due to any improvement in the patient's power to produce endogenous insulin, and can hardly be due to anything else than the condition of his stores of carbohydrate. While insulin was omitted, he excreted up to 140 grm. a day, more sugar than the total glucose equivalent of his diet, and no doubt must have emptied his store of carbohydrate almost completely. Thereafter insulin was almost normally effective in controlling his condition, presumably because his store was not filled to overflowing. One must imagine that by the previous period of overfeeding and high insulin (115 grm. C. and 250 units of insulin) his stores were full to their utmost capacity, and that the enormous doses of insulin had no effect in dealing with the excess of carbohydrate over the very limited amount he could store. (The efficacy of insulin acting on empty carbohydrate stores has been discussed elsewhere by the author (14).) Later in 1927, these 80 units of insulin proved insufficient to control his condition and he required an increase to 160 units a day in spite of the same diet strictly maintained. I believe that his insulin requirements could be reduced temporarily at any time by omitting insulin for a period, allowing him to lose his store of carbohydrate, and then restarting the insulin, but this experiment is rather too drastic to repeat, and requires too frequent rehospitalization. I have recently observed another insulin-resistant case who responded in the same way to the temporary omission of insulin by a great increase of carbohydrate tolerance. By an error, insulin was omitted for two days, and she went into profound coma. As a result, her glucose equivalent rose from a quarter of a grm. per unit to nearly 2 grm.

Summary and Conclusions.

A case of insulin resistance is described in a young diabetic man. The diabetes was severe from the onset in 1925, but was controlled by 40 units of insulin a day and a diet of 35 C., 38 P., and 83 grm. F. The fall in blood-sugar after insulin was normal at this time. A year later he required 100 units on the same diet, and six months later he was excreting 5 to 10 grm. of sugar on a diet of 60 C., 80 P., and 150 F., with 220 units of insulin, glucose-equivalent of 1 grm. per 2 units. When insulin was omitted he went into coma, so that insulin did act on him although to an unusually small degree. None of the usual factors, such as sepsis, &c., which make diabetics insulin resistant, was present in his case. Blood-sugar studies showed features quite different from the ordinary severe diabetic. His blood-sugar was lowest after a night's fast, and when carbohydrate was given the blood-sugar rose in spite of large doses of insulin. This was not due merely to a delayed insulin action or lack of absorption, because insulin, given in the fasting condition, reduced the blood-sugar at the usual rate, though to a less degree than in a 'normal' diabetic. It appears, therefore, in this case, that insulin cannot deal with ingested carbohydrate in the usual way,

by storing it as glycogen. Further evidence that he had little or no store of carbohydrate was obtained by starving him, when his blood-sugar fell spontaneously instead of rising, as in the usual severe diabetic when insulin is withheld. It is suggested that in this case insulin failed to store glycogen normally, but did have its other action of checking the new formation of sugar and ketones from endogenous protein and fat. It seems probable, therefore, that in him a factor other than insulin is lacking, perhaps some coenzyme which is necessary to the usual action of insulin in forming glycogen.

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TABLE I.

S. J.

Date.	Urine. Sugar.	Ketones.*	B.-Sugar.†	Diet. C.	P.	F.	Insulin (Units).	Weight in lb. and Remarks.
			%					Admitted to hospital
14.4.25	6 %	F. +	?				20 6-hrly.	90
10.5.25	0	0	0·166	—	—	—		
			0·110	36	38	83	20 b.d.	104. Normal.
			3 hrs.	30 cals. per kg.				Insulin action
Dec. 1925	—	Broke diet	—	—	—	—	20 b.d.	111
20.1.26	+ + +	F. +	0·285					
			0·187	30	57	45	30 & 20	Coryza and abdominal pain
28.1.26	0	R. tr.	—	—	—	—	30, 20, & 10	—
2.10.26	+ +	+ +	—	30	57	55	100	Precomatose
3.10.26	—	—	—	—	—	—	120	,,
4.10.26	+ + +	F. + +	—	40 grm. 2-hrly.			40 2-hrly.	,,
5.10.26	+ + +	F. + +	—	80 ,, ,,			80 2-hrly.	,,
6.10.26	0	0	—	—	—	—	—	Recovered
7.10.26	sl. tr.	0	—	80 grm. 4-hrly.			30 4-hrly.	—
8.10.26 to 13.1.27	tr.	tr.	0·170	115	81	150	250	114

* F = Ferric chloride. R = Rothera's test.
† Fasting blood-sugars underlined.

TABLE II.

Date.	Urine. Sugar.	Urine. Ketones.	B.-Sugar.*	Diet. C.	Diet. P.	Diet. F.	Insulin (Units).	Weight in lb. and Remarks.
In-patient.	Grm.		%					Transferred to K. C. Hospital.
13.1.27 to	55	R. + +	0·210	115	80	150	220	Ins. glucose 2/1
18.1.27			0·300	41 cals. per kg.				
18.1.27 to	5	R. sl. tr.	0·108					
24.1.27			0·230	60	,,	,,	220	114
25.1.27 to	140	F. + + +	0·379	,,	,,	,,	0	110. Precoma-
30.1.27								tose
23.1.27 to	11	—	0·160	50	75	150	120	114
3.2.27				37 cals. per kg.				
3.2.27 to	0	v. sl. tr.	0·109	,,	,,	,,	120	—
9.2.27								
9.2.27 to	0	0-sl. tr.	133	—	—	—	80	112
25.2.27			181					
25.2.27 to	77	F. + +	0·349	37 cals. per kg.			Synthalin	110. Precoma-
2.3.27								tose
3.3.27 to	0	—	0·100	,,	,,	,,	80	114
16.3.27			0·170					
Out-patient.								
May	+ +	tr.	0·331	,,	,,	,,	40 & 40	—
July '27	0	tr.	—				80 & 80	—
Readmitted.								
August '27	0	sl. tr.	0·130 &c.	,,	,,	,,	80 & 80	116

* Fasting blood-sugars underlined.

TABLE III.

No. 1.

Date:	13.1.27.	24.1.27.	25.1.27.	
Diet: 4 meals	C. 115, P. 80, F. 150.	C. 60, P. 80, F. 150.	C. 60, P. 80, F. 150.	
Insulin: 4 doses	60, 60, 60, 40.	100, 100, 100, 100.	0.	
Hours.	Blood-sugar.	Blood-sugar.	Blood-sugar.	R. D. L. 20 Units.
	%	%	%	%
8 a.m.	0·221	0·156 20 grm. C.	0·089	0·242
10 ,,	0·308	0·244	0·179	0·185
12 noon	0·272	0·232	0·224	0·097
4 p.m.	0·243	0·152	0·200	0·125
9 ,,	0·210	0·082	0·218	0·178 (6 p.m.)

TABLE IV.

No. 2.

Date:	15.3.27.	16.3.27.	25.8.27.	27.8.27.	26.8.27.
	Breakfast (20 C.).	Breakfast.	Breakfast.	Breakfast.	Breakfast.
	40 Insulin.		80 Insulin.		80 Insulin.
Hours.	Blood-sugar.	Blood-sugar.	Blood-sugar.	Blood-sugar.	Blood-sugar.
	%	%	%	%	%
0	0·127	0·155	0·094	0·152	0·132
1	0·155	0·179	—	—	—
2	0·178	0·217	0·131	0·193	0·168*
3	0·164	0·197	0·124	0·215	0·158*
4	—	—	0·113	0·197	0·132*

* Hard exercise.

TABLE V.

No. 3.

Date:	24.2.27.	30.8.27.	31.8.27.	10.9.27.	6.9.27.		12.9.27.
	40 Units Subcut.	40 Units Subcut.	40 Units Intrav.	10 Units Subcut.	0·5 mg. Ergotamine.		80 Insulin. mg. Inorg. P.
Hours.	Blood-sugar.	Blood-sugar.	Blood-sugar.	Blood-sugar.	Blood-sugar.	Pulse.	
	%	%	%	%	%		
0	0·133	0·162	0·150	0·123	0·143	72	5·4
$\frac{3}{4}$	0·104	0·136	0·123	0·127	0·139	60	—
$1\frac{1}{2}$	0·071*	0·113	0·088	0·131	0·117	54	4·8
$2\frac{1}{2}$	0·078	0·092	0·060*	0·108	0·117	60	—
$3\frac{1}{2}$	0·084	0·084	0·056	0·098	—	80	3·8

* Symptoms of hypoglycaemia.

TABLE VI.

No. 4.

Hours.	0	Ins. & Food.	2	4	6	10	14
	Blood-sugar.		Blood-sugar.	Blood-sugar.	Blood-sugar.	Blood-sugar.	Blood-sugar.
	%		%	%	%	%	%
S. J.	0·083	80 & 20 C.	0·128	0·088	0·054	0·057	0·086
R. D. L.	0·224	20 & 20 C.	0·171	0·089	0·089	0·090	0·321
Hours.	17	19	22	26	27	29	36
	%	%	%	%		%	%
S. J.	0·088	0·093	0·077	0·065	20 C.	0·169	0·207

OBSERVATIONS ON THE PULMONARY VENTILATION AND OXYGEN CONSUMPTION IN PULMONARY TUBERCULOSIS, AND ON THE EFFECT OF THE RESPIRATORY QUOTIENT ON THE RELATION BETWEEN PULMONARY VENTILATION AND OXYGEN CONSUMPTION [1]

By RAYMOND WILLIAMSON

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ONE effect of disease is to alter the metabolic processes of the body. The measurements required to determine such alterations generally involve delicate chemical procedures which can only be carried out in a well-equipped laboratory. In the present research I have endeavoured to study some of the problems of altered metabolism by a method which can be used in the wards of a hospital. The basis of these investigations is the respiratory exchange, and I have endeavoured to elucidate some of the conditions under which that exchange may be altered. I have considered three variable factors: (1) The pulmonary ventilation, the intensity of which is measured by estimating the amount of air expired in a unit of time (1 min.). (2) Changes in the composition of the expired air, measured by the amount of oxygen disappearing and the amount of carbon dioxide appearing when the composition of the air expired is compared with that inspired. (3) The respiratory quotient, which is the ratio between the oxygen absorbed and the carbon dioxide produced; this of course varies with the nature of the food-stuffs undergoing combustion, being unity for carbohydrates, 0·8 for proteins, and 0·7 for fats.

Haldane and Priestley (1) showed that the pulmonary ventilation varies with the production of carbon dioxide in the body. Boothby (2) has shown that the intensity of the pulmonary ventilation and the circulation rate both increase progressively with the oxygen consumption in a healthy subject; Newburgh and Means (3) have shown that the same relation holds for a subject with serious disease of the heart, and Krogh and Lindhard (4) that in induced work the pulmonary ventilation and oxygen consumption vary together. Assuming therefore, with Means (5), that 'other things being equal the pulmonary ventilation will be proportional to metabolic rate', I have measured the pulmonary ventilation with a view to determining the comparative variation of metabolic

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rate in health and certain diseased conditions. The investigation has shown that the relation between pulmonary ventilation and consumption of oxygen, though close, is modified to some extent by the respiratory quotient at the time of the experiment. It has shown also that the relation between pulmonary ventilation and oxygen consumption is different in a normal individual from one suffering from pulmonary tuberculosis.

Methods.

The technique employed was the Douglas bag method for the determination of the basal metabolic rate. It is unnecessary to describe it in detail, since a detailed description is given in many text-books. The Haldane gas-analysis apparatus was employed for the analysis of the expired air, and a Dautrebande mask was used in preference to a mouthpiece and a nose-clip. The principle of the method is simple. A mask, furnished with inspiratory and expiratory valves, is fitted closely over the patient's mouth and nose. The expiratory valve is connected with a large rubber bag by means of rubber tubing in which there is a two-way stopcock permitting the subject to expire into the surrounding air or into the bag as may be desired. When the mask is first adjusted the tap of the stopcock is turned so that the subject expires into the room; an interval is then allowed until the respirations become steady; then the tap is turned so that the patient breathes into the bag. The expired air is collected for a known time. It is then measured by passing it through a water gas-meter, and a sample of it is taken for analysis. The intensity of the pulmonary ventilation is found by dividing the quantity of expired air by the number of minutes during which it was collected.

A special room was not available in which to isolate the patient, but he was screened off from the rest of the ward half an hour before the commencement of the experiment and lay flat on his back during that period. The mask was adjusted and an interval of five minutes (or until the respirations were steady) was allowed before the sample of expired air was collected. This was collected over a period of five minutes. A sample was then taken for analysis and the amount of air in the bag measured.

The patients who were the subjects of these experiments were carefully chosen from the point of view of temperament as well as clinical condition: all were men of an intelligent, steady type who could and did co-operate willingly.

The experiments were made under two sets of conditions: one under basal conditions, the other at two different times during the day under certain definite conditions to be described later.

Basal conditions are those under which the subject is in a state of maximum physical and mental rest when the heat production and oxygen consumption are the minimum necessary to maintain the vital functions. The experiments recorded here as being made under basal conditions were carried out between

9 and 9.15 in the morning, the patient's last meal having been at 7 p.m. the previous evening. The patient was in as comfortable and restful a state as possible.

In the general routine of the hospital there are two 'rest hours'; every patient has to lie quietly on his bed between 11.15 and 12.15 (before lunch), and from 4.30 to 5.30 (after tea). These 'rest hours' were made use of to determine the intensity of the pulmonary ventilation and oxygen consumption after patients had performed a certain amount of work and during the metabolism of food. In the first rest hour the specimen of expired air was collected at 11.45, after the patient had rested for half an hour and two hours and a quarter after breakfast; the specimen for the second rest hour was collected at 5.15, after the patient had rested for three-quarters of an hour. This specimen was actually collected three-quarters of an hour after tea.

Grouping of the Experiments.

The experiments recorded fall into three groups:

1. Those in which repeated observations have been made on the same patient under basal conditions and over a fairly long period. The pulmonary ventilation and oxygen consumption having varied from time to time, it is possible to plot the one against the other to show the relationship between them.

2. Those in which three estimations of pulmonary ventilation and oxygen consumption have been made on the same day, the first determination being made under basal conditions.

3. A group of experiments on a healthy subject in which the determinations were made at various times during the day in order to obtain as many values for pulmonary ventilation and oxygen consumption as possible within the limits of an ordinary day's work.

Group I. Case 1. E. V. (physician, Dr. Cecil Bosanquet). Diagnosis: chronic pulmonary tuberculosis of several years' duration. Tubercle bacilli present. Extent: right, zones 1 and 2; left, zones 1, 2, and 3. Stage: cavities in left upper zone; fibrosis marked; compensatory emphysema of right lung. Type: febrile on admission, becoming afebrile under treatment. Progress: marked improvement, gain in weight.

Case 2. J. P. (physician, Dr. Cecil Wall). Diagnosis: chronic pulmonary tuberculosis with old right pleurisy of several months' duration. Tubercle bacilli present. Extent: right, zone 2; left, zones 1, 2, and 3. Stage: cavities in left upper zone, some fibrosis, compensatory emphysema of right lung. Type: afebrile. Progress: improved, gained weight.

Case 3. R. P. (physician, Dr. L. S. Burrell). Diagnosis: pulmonary tuberculosis of several months' duration with a small effusion at the left base. Onset with broncho-pneumonia complicating appendicectomy. Tubercle bacilli absent at onset of illness but present later. Extent: right, scattered infiltration, zones 1, 2, and 3; left, zones 1 and 2. Pleural thickening right base, small effusion

TABLE I.

Quantity and Quality of Expired Air under Basal Conditions for four Patients with Pulmonary Tuberculosis and one with Non-Tuberculous Pulmonary Fibrosis.

Subject.	Date.	Litres of Expired Air per min. (Pulm. vent.)	O_2 consumed per min. c.c.	CO_2 produced per min. c.c.	Respiratory Quotient.
Case 1. E. V.	6.11.26	7·717	284	192	0·68
	12.11.26	6·757	266	175	0·66
	18.11.26*	8·129	372	210	0·56
	27.11.26	7·138	255	178	0·70
	7.12.26	7·794	284	205	0·72
	13.12.26	7·258	268	188	0·70
	22.12.26	6·300	228	171	0·75
	6.1.27	5·967	216	184	0·85
	17.1.27	5·070	187	129	0·74
	18.1.27	5·094	189	136	0·72
	25.1.27	6·289	218	175	0·80
	30.1.27	6·686	252	176	0·70
	8.2.27	6·484	232	190	0·82
Case 2. J. P.	2.12.26	7·747	289	235	0·81
	4.12.26	7·376	288	217	0·75
	14.12.26	6·768	251	195	0·78
	7.1.27	6·410	255	201	0·79
	15.1.27	5·921	222	176	0·79
	22.1.27	7·319	280	210	0·75
Case 3. R. P.	4.2.27	9·297	301	218	0·72
	7.2.27	9·116	289	193	0·70
	18.2.27	7·332	229	166	0·72
	23.2.27	7·338	241	197	0·82
	2.3.27	6·984	225	184	0·81
	9.3.27	7·249	243	194	0·80
	17.3.27	6·912	221	175	0·79
	30.3.27	7·458	228	180	0·79
	25.4.27	7·428	220	214	0·97
Case 4. E. M.	5.2.27	9·614	284	214	0·75
	7.2.27	9·476	279	208	0·74
	19.2.27	9·546	280	203	0·72
	23.2.27	10·173	298	237	0·79
	2.3.27	9·501	269	201	0·74
	10.3.27	8·012	242	195	0·80
	17.3.27	8·444	261	184	0·70
	31.3.27	8·321	226	194	0·85
	7.4.27	7·521	223	220	0·99
	11.4.27	7·100	256	187	0·73
	25.4.27	6·832	251	176	0·70
	4.5.27	7·593	257	181	0·70
Case 5. F. O. W.	1.9.26	7·194	314	253	0·80
	25.10.26	8·728	338	299	0·85
	10.11.26	7·322	329	248	0·72
	20.11.26	6·310	279	245	0·87
	30.11.26	5·202	246	203	0·82
	6.12.26	5·191	256	194	0·75

* The patient vomited during the night and in the morning he had a temperature of 101.6 F., with signs of extension of the tuberculous process on the left side. The temperature became normal and his condition began to improve in about a week. The sputum was increased in quantity.

left base. Type: febrile on admission, becoming afebrile later. Progress: some improvement, increase in weight.

Case 4. E. M. (physician, Dr. L. S. T. Burrell). Diagnosis: chronic pulmonary tuberculosis of about a year's duration. Tubercle bacilli present. Extent: right, zones 1, 2, and 3; left, zones 1 and 3. Stage: marked fibrosis, cavities in both upper zones. Type: febrile. Progress: temperature improved, otherwise condition remained unchanged.

Case 5. F. O. W. (physician, Dr. Cecil Wall). Diagnosis: non-tuberculous fibrosis of the lower right lobe of several years' duration. Tubercle bacilli absent. Extent: right lung, zones 2 and 3, marked fibrosis and pleural involvement, cavities seen in perihilar region on X-ray after lipoidol injection. Type: febrile with much foul sputum. Progress: after a bronchoscopic examination by Mr. Tudor Edwards the patient brought up a large quantity of pus and continued to expectorate 6 to 8 oz. daily for some weeks, but he became afebrile, and later his sputum decreased and he made a marked improvement.

The results of the examinations made on the above cases are given in Table I, and the pulmonary ventilation and oxygen consumption are plotted in Figs. 1 to 5. The general direction of the curves shows that the pulmonary ventilation increases progressively with oxygen consumption.

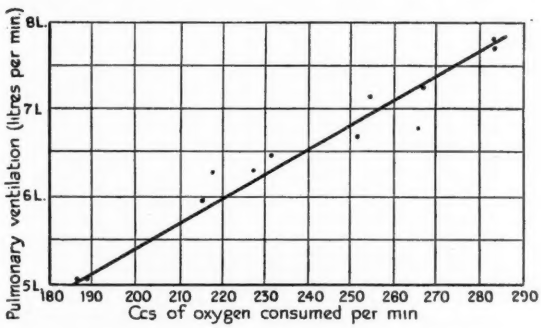

FIG. 1. Case 1. E. V. Pulmonary tuberculosis.
[Relation between the consumption of oxygen and pulmonary ventilation.]

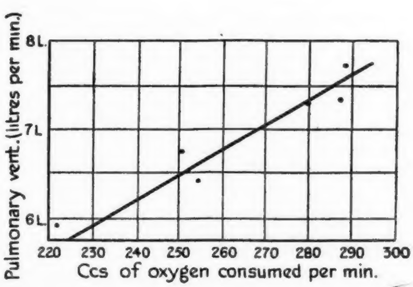

FIG. 2. Case 2. J. P. Pulmonary tuberculosis.
[Relation between the consumption of oxygen and pulmonary ventilation.

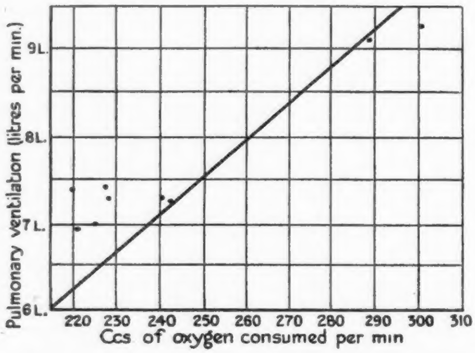

FIG. 3. Case 3. R. P. Pulmonary tuberculosis.
[Relation between the consumption of oxygen and pulmonary ventilation.]

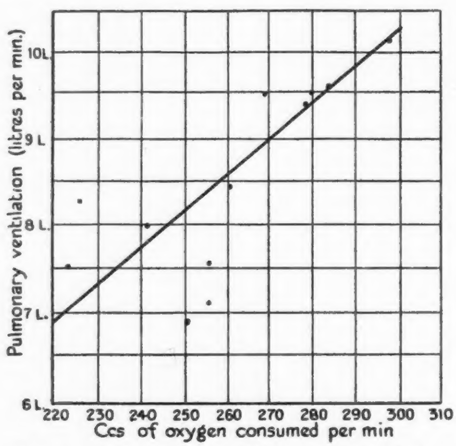

FIG. 4. Case 4. E. M. Pulmonary tuberculosis.
[Relation between the consumption of oxygen and pulmonary ventilation.]

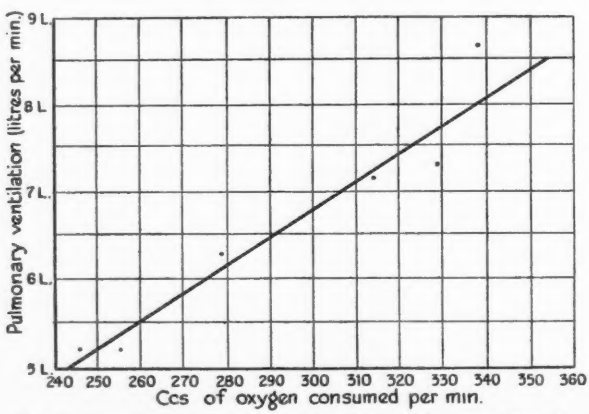

FIG. 5. Case 5. F. O. W. Non-tuberculous pulmonary fibrosis.
[Relation between the consumption of oxygen and pulmonary ventilation.]

Group II. Case 6. A. B. (physician, Dr. L. S. T. Burrell). Diagnosis: chronic pulmonary tuberculosis of several years' duration. Tubercle bacilli present. Extent: right, zones 1 and 2; left, zones 1, 2, and 3. Stage: marked fibrosis. Type: afebrile. Progress: good.

Case 7. J. R. (physician, Dr. L. S. T. Burrell). Diagnosis: pulmonary tuberculosis with right artificial pneumothorax. Tuberculosis of several years' duration. Tubercle bacilli present. Extent: right lung collapsed; left, zone 2. Type: afebrile. Progress: good.

TABLE II.

Quantity and Quality of Expired Air of four Tuberculous Patients: (1) under Basal Conditions, (2) before Lunch, (3) after Tea.

Subject.	Date.	Litres of Expired Air per min. (Pulm. vent.).	O_2 consumed per min.	CO_2 produced per min.	Respiratory Quotient.	Remarks.
			c.c.	c.c.		
Case 6.	6.4.27	6·988	224	173	0·77	Up six hours
A. B.		8·437	261	235	0·90	
		8·601	266	248	0·94	
Case 3.	17.3.27	6·912	221	175	0·79	In bed all day
R. P.		8·817	270	223	0·82	
		9·491	294	273	0·93	
Case 4.	11.4.27	7·100	256	187	0·73	In bed all day
E. M.		7·522	271	217	0·80	
		8·871	294	238	0·81	
Case 7.	7.4.27	6·145	253	208	0·82	Up two hours
J. R.		7·184	294	268	0·91	in the after-
		7·823	304	284	0·93	noon

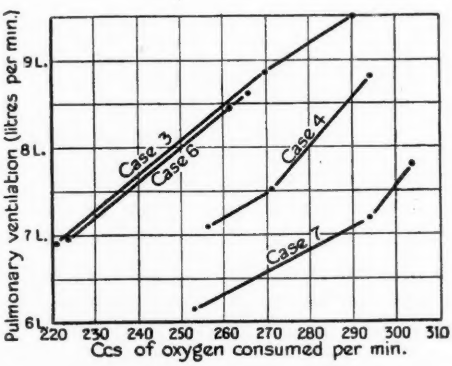

FIG. 6. Tuberculous subjects.
[Relation between oxygen consumption and pulmonary ventilation for four tuberculous subjects.]

Table II gives the pulmonary ventilation and the oxygen consumption at different times on the same day for four cases of pulmonary tuberculosis. These are shown graphically in Fig. 6. The curves are of the same type as in the previous diagrams; the pulmonary ventilation and oxygen consumption vary together.

TABLE III.

Quantity and Quality of Expired Air for Normal Subject under Varying Conditions.

Experiment.	Date.	Litres of Expired Air per min. (Pulm. vent.).	O_2 consumed per min. c.c.	CO_2 produced per min. c.c.	Respiratory Quotient.	Remarks.
1	1.4.27	5·515	223	170	0·76	Conditions comparable to those under which experiments in Table II were performed.
		6·144	287	205	0·71	
		7·025	325	237	0·71	
2	11.4.27	6·095	249	194	0·77	
		6·504	282	207	0·73	
		8·055	343	264	0·77	
3	12.4.27	5·256	235	167	0·71	
		6·256	292	208	0·71	
		7·294	323	243	0·75	
4	20.4.27	5·804	252	181	0·72	
		6·530	299	217	0·70	
		6·622	301	219	0·72	
5	14.6.27	5·325	235	165	0·70	Basal conditions 7.30
		6·862	293	222	0·76	After tea 5.30
6	17.6.27	5·290	233	166	0·72	Basal conditions 7.30
		6·957	302	229	0·75	After breakfast 9.15
		6·782	293	222	0·76	Before lunch 11.45
		7·103	310	237	0·76	After lunch 2.30
		6·281	286	219	0·77	Before tea 4.15
		7·425	266	237	0·88	After tea 6.15
		6·391	253	200	0·75	7.15
		6·619	259	207	0·80	8.30
7	20.6.27	4·764	197	130	0·67	Basal conditions 7.20
		5·922	224	178	0·79	Before breakfast 8.5
		6·890	292	230	0·78	After breakfast 10.30
		6·346	271	190	0·70	Before lunch 12.45
		7·523	311	247	0·79	After tea 5.30
8	22.6.27	4·881	207	145	0·70	Basal conditions
		6·113	241	187	0·78	Before breakfast 7.50
		6·920	297	214	0·72	Before lunch 12.45
		7·553	331	244	0·74	After tea 5.50
9	23.6.27	7·497	295	243	0·82	After breakfast 9.15

Group III. Experiments 1 to 4 in Table III were carried out on a normal subject under similar conditions to those given in Table II for tuberculous patients. The first sample was taken under basal conditions, the second before lunch, and the third about an hour after tea. Half an hour's rest, lying flat on a camp bed, was observed before each experiment. The relation between pulmonary ventilation and oxygen consumption is shown graphically in Fig. 7. There are four curves running almost parallel, but at different levels. The experiments were made within a period of three weeks on the same subject, and it was difficult to understand the variation in the levels of the curves. In order to find an explanation another series of experiments was made, the samples being taken at various times during the day in order to obtain as many intermediate points for the intensity of the pulmonary ventilation and oxygen consumption as possible. These experiments, 5 to 9, are given in Table III, and are plotted in Fig. 8, together with the results of Experiments 1 to 4. The value of the respiratory quotient is indicated in each case. Here again all

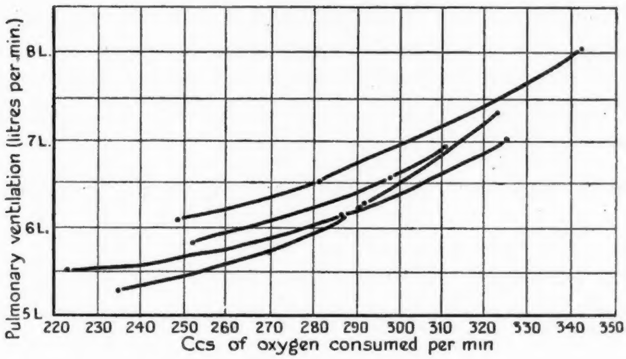

FIG. 7. Normal subject.
[Relation between the consumption of oxygen and pulmonary ventilation for normal subjects.]

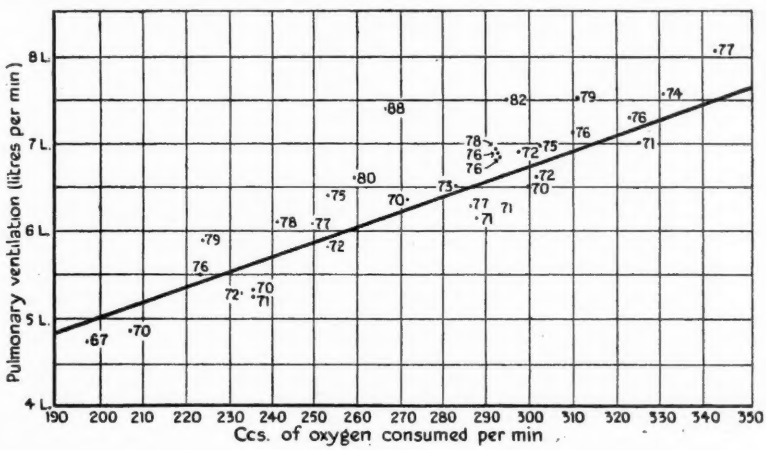

FIG. 8.
[The relation between oxygen consumption and pulmonary ventilation, the values of the respiratory quotient for each particular experiment being indicated.]

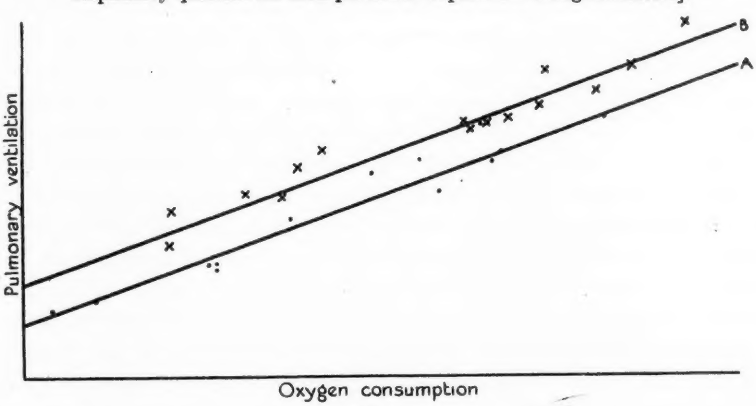

FIG. 9.
[The relation between oxygen consumption and pulmonary ventilation.]
•, Respiratory quotients 0·67 to 0·73 are plotted round line A, average R.Q. 0·71.
×, „ „ 0·74 „ 0·80 „ „ „ „ B, „ „ 0·77.

the points are arranged round a straight line, but there is considerable deviation from that line. It was felt that the deviation was far too great to be accounted for by any error of technique, and, further, it was noted that the figures for the respiratory quotients are arranged in a definite manner. They fall roughly into two groups:

	Group 1.					Group 2.						
R. O.	0·67	0·70	0·71	0·72	0·73	0·74	0·75	0·76	0·77	0·78	0·79	0·80
Number	1	4	4	4	1	1	3	4	3	2	2	1

Two others, a 0·82 and 0·88, are disregarded.

When these two groups are plotted separately, as in Fig. 9, it is found that the points in each group lie much nearer to a line drawn through them, and, further, the line passing through the second group is higher, but parallel to that through the first group. It follows that the resultant of the oxygen consumption and pulmonary ventilation is a narrow band rather than a straight line, this band being composed of a series of lines one above the other, each corresponding to a particular respiratory quotient.

Discussion.

We have offered evidence to show that there is a definite relationship between oxygen consumption, the intensity of pulmonary ventilation, and the respiratory quotient, the pulmonary ventilation being only approximately a linear function of the oxygen consumption. Under certain circumstances, however, when there is no very marked difference in the respiratory quotients, the relation between oxygen consumption and pulmonary ventilation is so close as to make the measure of the pulmonary ventilation a useful clinical method for following the changes in the metabolic activity of the same patient over a period of time. This is a question which we hope to treat more fully in another communication.

In Figs. 3 and 4 there is a considerable variation in the degree of accuracy with which the points plotted fall on a straight line. This may be due to: (1) Variation in the respiratory quotient from time to time. (2) Alteration in the rate of pulmonary ventilation due to nervous or physical factors. Cases 3 and 4 were more ill than the others. (3) Improvement in the condition of the patient during the period under investigation. We have a little evidence suggesting that a definite alteration in the relation of oxygen consumption to pulmonary ventilation may take place as a patient improves or gets worse.

Fig. 6 shows that, in the tuberculous cases considered, individual differences occur in the relation between the pulmonary ventilation and the oxygen consumption, but there is a remarkable correspondence in the steepness of the curves in each case. The steepness of these curves also shows a close correspondence with those of Figs. 1 to 5, especially Cases 3 and 4, curves for which are given in the two groups. Table IV gives the average of the pulmonary ventilation and oxygen consumption of the four tuberculous cases in Table II, and the average of the four comparable examinations on the normal subject (Experiments 1 to 4, Table III).

TABLE IV.

	Litres of Expired Air per min.	Oxygen consumed per min.	
Tuberculous subject	6·811	238	Basal conditions
	7·990	274	At 11.45 a.m.
	8·696	290	At 5.15 p.m.
Normal subject	5·530	239	Basal conditions
	6·358	290	
	7·249	323	

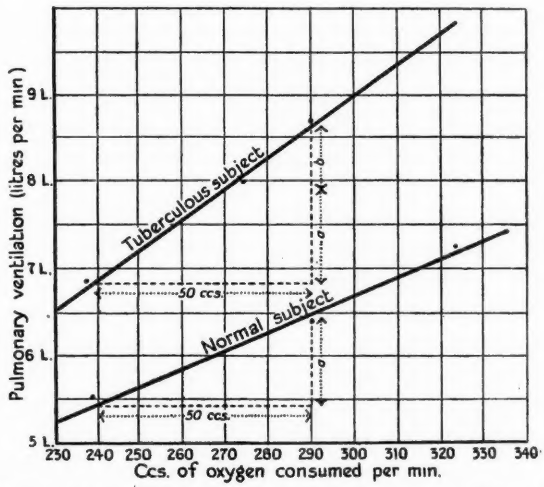

FIG. 10. Diagram showing the relation between oxygen consumption and pulmonary ventilation in a normal and a tuberculous subject.

[For an increased oxygen consumption of 50 c.c. per min. (from 240–290 c.c. per min.), the pulmonary ventilation of a normal subject is increased by the amount a, that of the tuberculous subject by the amount $a+b$. Note also that the tuberculous subject began at a higher rate of pulmonary ventilation than the normal.]

Both in normal subjects and in tuberculous subjects the increased oxygen consumption is associated with increased pulmonary ventilation, but in tuberculous subjects the rate of increase of the pulmonary ventilation is greater than in normal subjects. This is shown graphically in Fig. 10, which is constructed from the data given in Table IV. In the tuberculous patient the curve is steeper and commences at a higher level than in the case of the normal subject. This is an important factor in the occurrence of dyspnoea in pulmonary tuberculosis. Consider what happens when there is an increase in oxygen consumption from 240 to 290 c.c. per min. The normal subject commences with a pulmonary ventilation of 5·450 litres per min., while the tuberculous patient begins with a pulmonary ventilation of 6·850 litres per min.; at 290 c.c. of oxygen consumption per min. the normal subject has increased his ventilation to 6·500 litres per min. and the tuberculous subject to 8·650 litres per min. For an amount of work involving an increase of 50 c.c. in the oxygen consumption per min. the tuberculous patient has not only to begin at a higher level of pulmonary

ventilation, but he has to increase his ventilation by 0·75 litres per min. more than the normal subject. For a higher oxygen consumption this increase will be proportionally greater. It is obvious that dyspnoea must occur sooner in a tuberculous patient than in the normal. The reduced vital capacity and the increased dead space are of course additional factors in the onset of dyspnoea in tuberculous patients.

Conclusions.

1. Oxygen consumption and pulmonary ventilation in patients with pulmonary tuberculosis when examined over a considerable period under basal conditions vary together: the results of the experiments when plotted out graphically give a curve approximating to a straight line (Figs. 1 to 5).

2. Even under varying conditions there is an approximately direct relationship between the oxygen consumption and pulmonary ventilation (Figs. 6 and 7).

3. Experiments on a normal subject show that there is a relationship between oxygen consumption and pulmonary ventilation which is close under basal conditions, but not so close under other conditions, being considerably modified by the respiratory quotient. The results of the experiments when plotted out show that the points do not fall on a straight line, but within a narrow band, their position in the band depending on the respiratory quotient.

4. For practical purposes the relationship between oxygen consumption and pulmonary ventilation seems sufficiently close to permit the assumption that the measure of pulmonary ventilation indicates the rate of metabolism. It is suggested that in pulmonary tuberculosis measurements of the pulmonary ventilation at intervals under similar conditions may be a useful method of investigating the progress of the patient.

5. For the same amount of work a greater pulmonary ventilation is required by a tuberculous subject than by a normal one, and in consequence dyspnoea will ensue earlier in the tuberculous subject.

The work described above has been done under the auspices of the Will Edmonds Clinical Research Committee, to whom my best thanks are due. I am also indebted to the Medical Committee of the Hospital for Consumption and Diseases of the Chest, Brompton, for permission to make full use of their cases for investigation, and also for providing me with laboratory accommodation.

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THE CLINICAL IMPORTANCE OF VARIATIONS IN THE NUMBER OF CUSPS FORMING THE AORTIC AND PULMONARY VALVES[1]

By GLADYS M. WAUCHOPE

Pathogenesis.

In the human embryo the aortic and pulmonary arteries are formed by division of the truncus arteriosus, the forepart of the early tubular heart. The dividing septum, developing from the distal end, reaches four endocardial cushions, an anterior, a posterior, and two lateral, and bisects each of the lateral thickenings, thus forming six rudimentary cusps, three at the pulmonary orifice and three at the aortic.

Alterations in this symmetrical arrangement occur from time to time, either valve being composed of two, four, or even five cusps. Dilg (1) collected from the literature the following variations:

2 aortic cusps	23 cases
2 pulmonary cusps	64 ,,
4 aortic cusps	2 ,,
4 pulmonary cusps	24 ,,
5 aortic cusps	1 ,,
5 pulmonary cusps	2 ,,

De Vries (2) from 3,600 necropsies gives the following instances:

2 aortic cusps	12 ,,
2 pulmonary cusps	3 ,,
4 aortic cusps	1 ,,
4 pulmonary cusps	9 ,,
Combined case (i.e. two aortic cusps with three uneven pulmonary, one being rudimentary)	1 ,,

Irregularities in the growth of the aortic septum would account for cases in which there are only two cusps, one or both lateral cushions remaining undivided. The bicuspid condition of both valves occurred in one case in this series (Table I, 4 and Table III, 51), in two of Dilg's (1), and in one of Osler's (4), but more frequently one valve only is composed of two cusps, the other being normal. The fourth and fifth cusps appear to be developed later and are usually rudimentary.

[1] Received December 6, 1927.

No record has been found of cases in which two aortic cusps are compensated for by four pulmonary, and vice versa. Often in the bicuspid valve one of the cusps is larger than the other and appears to be formed by union between two; the question therefore arises whether these numerical abnormalities are due to maldevelopment, to foetal endocarditis, or to postnatal endocarditis. De Vries (2) considered that all cases in which the pulmonary valve is affected are due to maldevelopment, as also are the cases in which more than three cusps are present in either valve. The latter proposition will not be disputed, and there is considerable evidence in favour of considering the bicuspid pulmonary valve to be due to an error in development. In the first place other congenital defects are usually present; thus in Dilg's (1) list of 64 collected cases, in 56 the ventricular septum was defective and in 37 there was narrowing of the pulmonary orifice—only in 3 was no additional abnormality of the heart or pulmonary artery observed. Secondly, the valves are usually thin and transparent and show no sign of a past inflammatory process.

The congenital origin of the aortic bicuspid valve is not so well established, but Lewis and Grant (3), having examined serial sections in eleven cases, conclude:

1. That the condition occurs as an error in development.

2. That there is no evidence that foetal endocarditis produces fusion of the cusps.

3. That cases in which the condition occurs as a congenital defect may be distinguished from those in which fusion of two cusps is brought about by postnatal endocarditis, the most important point of distinction being the architecture of the cusp seen under the microscope. In the subdivided cusp the layers pass uninterruptedly from one side to the other, but where fusion is due to inflammation the structure of the normal valve can be traced.

The evidence is thus in favour of the view that all variations from the usual number of cusps in the aortic and pulmonary valves arise as maldevelopments.

Clinical importance.

These variations have become clinically important owing to the observation that even minor deviations from the normal in the structure of the cardiac valves seem to render the heart more susceptible to infection. Osler (4) in 1886 described eighteen cases of bicuspid aortic valve and pointed out the importance of the condition in the aetiology of ulcerative endocarditis, and this association has been fully recognized by physicians dealing with subacute infective endocarditis (endocarditis lenta) in soldiers during and after the late war. Horder (5), who discussed the question in the Lumleian lectures in 1926, was led to the conclusion that a detailed study of small abnormalities, of the aortic valves particularly, would probably show that they are more important as a predisposing factor in infective endocarditis than has hitherto been suspected.

The Pulmonary Valve.

Less attention has been paid to numerical variations in the pulmonary cusps, because they are usually combined with other and more severe congenital lesions and are not in themselves an important predisposing factor in acquired disease; moreover, acquired infection of the pulmonary valve is not common. Inflammation or sclerosis was noted only 14 times in Dilg's 64 cases of bicuspid pulmonary valve, while among the 24 instances with four cusps there was no acquired abnormality of this valve.

Graves (9) published in 1843 'A remarkable case, presenting the Pulmonary Artery with only two valves, both highly inflamed and covered with Lymph, Hydro-Pericardium, Pneumonia, &c., &c.', which is interesting in view of the rarity of infection of the pulmonary valve apart from gross congenital malformation. A man of 66 was admitted to the Meath Hospital in 1841 'labouring under pneumonia'. 'There was complete absence of fever,' but 'cough, with prune-juice expectoration', was present, together with signs of consolidation at the base of the right lung. For seventeen days the physical signs remained almost stationary, but the patient suffered from thirst and his tongue became red and dry. He then died suddenly from, as it proved, pulmonary embolism. The relevant findings at necropsy were that there were two cusps only in the pulmonary valve and that 'they were both coated with a recent deposit of lymph, in some situations almost ¼ inch thick'. The valves themselves were 'much thickened and opaque, in this respect contrasting in a very remarkable manner with the valves of the aorta, which were quite free from disease'. 'There was some calcareous deposit on the tricuspid and mitral valves, but not to an extent beyond what is frequently found in subjects of the same age.'

Nine cases of abnormality in the pulmonary valve found in the London Hospital records conform with what is usually observed. Associated congenital lesions were common. In five of the cases the valve was bicuspid (Table I), and in all of these other congenital malformations were present, the heart or large vessels being affected in four, while among the four cases with four cusps (Table II) there was one of stenosis and one of dilatation of the pulmonary artery. Moreover, the abnormality of the pulmonary valve does not seem to have predisposed it to acquired disease, for, with the exception of the case of pulmonary stenosis (Table II, 4), in one case only (Table II, 2) was the pulmonary valve thickened at its margin, whereas endocarditis involving other valves occurred in two cases. In one of these a streptococcal endocarditis supervened on a previous rheumatic infection of the mitral valve (Table II, 1), while in the other the aortic, mitral, and tricuspid valves were affected by rheumatic endocarditis, leaving the bicuspid pulmonary valve clear (Table I, 2).

The Aortic Valve.

The bicuspid aortic valve is the most interesting of the minor variations, and this study of fifty-two unpublished cases has been made in the hope of providing

evidence as to how far it is of importance in the aetiology of acquired cardiac disease, particularly of endocarditis lenta.

Frequency.

In the London Hospital post-mortem room 52 cases of bicuspid aortic valve, considered to be of congenital origin, have been noted in the years 1912 to 1926 inclusive, among 9,966 necropsies performed on patients dying from all causes. Observations as to the frequency of the condition vary, and may be tabulated as follows:

TABLE A.

Source.	No. of Cases.	No. of Necropsies.	Ratio.
Babes (6)	7	10,000 (about)	1 in 1,429
De Vries (2)	12	3,600	1 „ 300
London Hospital	52	9,966	1 „ 192
Lewis and Grant (3)	3	215*	1 „ 71
Osler (4)	18	800 (over)	1 „ 45
Total	92	24,581	

* Lewis and Grant excluded cases of subacute infective endocarditis where they found the condition more frequently.

The combined figures give a proportion of 1 in 267, or about 3·6 per thousand.

Sex Incidence.

The sex incidence is strikingly unequal, the condition being found more frequently in the male. Among the cases collected by Lewis and Grant (3) there were 63 males and 20 females, while of the present cases 42 of the patients were male and only 10 female, in a series of necropsies which comprised 6,124 males to 3,842 females. The incidence of the bicuspid aortic valve was therefore 6·9 per thousand in men and 2·6 per thousand in women, a preponderance which may have some bearing on the association between the abnormality and endocarditis lenta, a disease more common in men than in women.

Condition of the Cusps.

A variety of conditions is found in the cusps of these valves. There may be two more or less equal cusps with no sign of subdivision or fusion. Both coronary arteries may arise above one of these cusps or one artery above each. More frequently one cusp is larger than the other, with a subdividing ridge on the larger cusp. Any two of the three normal cusps may be fused. The various conditions found in the London Hospital cases are shown in Table B.

Cases in which the anterior and left posterior cusps, i.e. the cusps below the orifices of the coronary arteries, were fused form the largest class, while fusion of the right and left posterior cusps occurred but rarely. Lewis and Grant (3) record that the commissure between the coronary cusps (in their terminology

right and left anterior) was affected twice as often as that between the anterior and right posterior cusps, and the third commissure seldom.

TABLE B.

Description of Cusps.		Cases.
Incomplete separation or fusion of anterior and left posterior cusps	11	15
Two cusps—one anterior, one posterior	4	
Incomplete separation or fusion of anterior and right posterior cusps		12
Two cusps—one right, one left		2
Incomplete separation or fusion of right and left posterior cusps		3
Three cusps joined		4
'Two aortic cusps,' position not stated		16

Other Congenital Lesions.

Associated with the aortic bicuspid valve other congenital malformations were observed in eleven cases (Table III, 3, 15, 17, 23, 30, 40, 41, 42, 48, 51, 52). In nine of these the heart or aorta was affected, with or without lesions in other parts of the body. Two (15 and 30) had malformations of the kidneys and urinary tract with no heart lesion except the bicuspid valve. Three (23, 40, 41) only presented fenestration of the aortic cusps, one in association with a Meckel's diverticulum (23). One had a bicuspid pulmonary valve and double inferior vena cava (51). There was one case of pulmonary stenosis (17), one with patent interventricular septum (48), and one case in a child of 11 months (3) of patent ductus arteriosus associated with a Meckel's diverticulum. Two cases showed constriction of the aorta at the site of the obliterated ductus arteriosus (42, 52); in one of these (52) the interventricular septum was defective. Lewis and Grant (3) remarked on the frequency with which constriction or coarctation of the aorta occurs in cases of aortic bicuspid valve, while Parkes Weber (7), discussing 'stenosis of the aortic isthmus', notes the association of the two conditions from this point of view.

Thickening of the Cusps.

Thickening at the site of fusion of two cusps or nodules at the valve margins were observed in thirteen cases. In four children, the eldest being four years old, the thickenings are described as 'gelatinous cushions' (Table III, 3, 26, 37, 49). In one (49), a child of four months, there was no subdivision of either cusp and the cushions were on the free margin of each cusp. Here at least it is clear that the cushions or nodules do not represent the result of prenatal or postnatal inflammation fusing two cusps, but are probably part of the congenital malformation. In the remaining nine cases in adults (Table III, 2, 5, 19, 20, 32, 36, 44, 50, 51) the origin of the thickening is doubtful. In Case 2 the margins of the mitral valve were thickened as well as the margins of the aortic, possibly as the result of a slight postnatal endocarditis. The patient was forty-two years of age. In

four cases (19, 5, 20, 32) the larger double cusp alone was affected, while in one (50) the smaller cusp only showed slight thickening at its margin. It is probable that the gelatinous cushions present in young children become fibrotic in later years, the line of fusion of two cusps being also subject to fibrosis.

Atheroma.

An exceptional degree of atheroma was found in two cases (Table III, 1, 43); both patients were women, one aged 37 and the other 62. In the latter case the atheroma had led to aortic stenosis. Calcareous nodules were found in four other cases (Table III, 4, 18, 27, 31). In Case 4 a calcareous patch occurred in the position of the absent septum between the fused cusps. In Case 27 there was fibrotic thickening in addition to calcification, and in Case 31 the signs of chronic rheumatic endocarditis. The ages of the patients in whom this calcification occurred were all over forty.

Before considering the incidence of infection on the bicuspid valve we may summarize the foregoing observations:

1. Other congenital malformations were associated with the bicuspid aortic valve in 21·1 per cent. of the cases in this series; in 17·3 per cent. the heart or aortic isthmus was malformed, but in three of these fenestration of the cusps was the only other cardiac abnormality; if these are excepted the percentage showing more definite malformation was 11·6.

2. Gelatinous cushions were present on the margins of the valve in four children, but in no adult patients.

3. Degenerative conditions of the aortic valve—fibrous thickening, atheroma, and calcification—occurred in 28·8 per cent. of the cases.

Osler (8) quotes statistics of 'sclerotic chronic endocarditis', a title which seems to apply to these conditions but covers also the late results of rheumatism. The figures are based on between 12,000 to 14,000 necropsies and the percentage ranged from 4 to 9, and includes all valves. The bicuspid valve has therefore probably increased the incidence on the aortic valve in the cases under review.

Endocarditis.

Turning now to infections of the aortic valve.

(*a*) Syphilitic aortic endocarditis occurred in two cases (Table III, 24, 34). Both patients were males; one (24) died at the age of forty-nine from the direct effects of the heart lesion, the other, also at forty-nine, from lobar pneumonia. Syphilitic aortitis in the first case implicated the whole of the thoracic and the upper part of the abdominal aorta; in the second case, the ascending aorta, aortic arch, and upper ten centimetres of the descending aorta. Inasmuch as syphilis of the aortic valves is usually due to an extension from the aorta, the involvement of the valves in these two cases cannot be accepted as evidence that the congenital abnormality rendered them exceptionally liable to infection.

(*b*) Rheumatic endocarditis was found five times (Table III, 6, 16, 31, 33, 46). The aortic valve was affected in all the cases, once alone (16), and in one case (31) to a greater extent than the mitral, which was affected four times. The incidence on the aortic valve is therefore greater than is usual in rheumatic endocarditis, where the mitral is generally the first to be attacked and the more severely damaged. In 416 cases of rheumatic endocarditis taken from the London Hospital records the incidence on the valves was as follows:

TABLE C.

	Cases.
Aortic and mitral	153
Mitral alone	118
Mitral, aortic, and tricuspid	109
Mitral and tricuspid	20
All four valves	9
Aortic alone	6
Aortic and tricuspid	1

The mitral, with or without other valves, was involved in 409 cases. The aortic was affected 278 times.

(*c*) Infective endocarditis supervened in seven cases (Table III, 38, 39, 42, 45, 47, 48, 52). One of these (48) was a case of acute pneumococcal endocarditis in a girl of nineteen years of age. The tricuspid valve only was infected, the two cusps of the aortic valve being thin and transparent. This case, therefore, need not be further considered. In the remaining six cases the aortic valve was affected. In five (39, 42, 45, 47, 52) the infection was of the subacute or chronic type known as endocarditis lenta. One patient (45) was a woman, aged 32, whose illness was of four and a half months' duration. There was no history or evidence of previous rheumatism, and a non-haemolytic streptococcus was cultured from the blood. Necropsy showed that both cusps of the aortic valve were covered with vegetations which had spread to the aortic cusp of the mitral valve. In two of the subjects (42 and 52) there was constriction of the aorta; one (52) had other congenital cardiac malformations, the other had served in France during the war. The two remaining subacute cases (39 and 47) occurred in ex-soldiers and were typical of the endocarditis lenta seen after the war.

The seventh case of infective endocarditis (38) was intermediate between the acute disease and endocarditis lenta, but in the following statistics it has been classified as 'acute infective endocarditis', as it is important to distinguish it from the true subacute form. The patient was a man of thirty-four years of age, who had served in France; his illness was of slightly less than three months' duration; necropsy revealed flat fibrinous vegetations, producing a few perforations, on the aortic cusps and a small area of haemorrhagic necrosis in the myocardium. The spleen was enlarged (1 lb. 2 oz.), soft, and contained a recent purulent infarct with several haemorrhagic infarcts of longer duration; one of these showed, on microscopic examination, an organized embolus. There were similar infarcts in the kidney and signs of haemorrhagic nephritis. A haemorrhagic abscess had formed at the entrance of a branch of the coeliac axis. Streptococci were demonstrated in films from the aortic valve.

In two of the cases (38, 39) the aortic valve alone was infected; in three (42, 45, 47) the vegetations had spread to the mitral valve, but were more abundant on the aortic. In the remaining case (52), in which there was a patent interventricular septum and coarctation of the aorta, the posterior pulmonary cusp was affected in addition to the aortic and mitral valves. The mitral in these cases never appeared to be the primary site of infection.

It is believed that infective endocarditis of the subacute and chronic types attacks chiefly the aortic valve, just as rheumatism appears to have a predilection for the mitral, but in 119 cases of endocarditis lenta collected from the London Hospital records the distribution on the valves was as follows:

TABLE D.

		Cases.
(1)	Aortic and mitral	75
(2)	Mitral valve alone	23
(3)	Aortic valve alone	13
(4)	Aortic, mitral, and tricuspid	5
(5)	Aortic and tricuspid	2
(6)	All four valves	1

The mitral valve was affected in 104 cases, the aortic in 96.

A comparison of the two tables C and D gives the following proportions:

Valves affected.	Percentage of Cases in Rheumatism.	Percentage in Endocarditis lenta.
Mitral, with or without other valves	98	87·4
Mitral alone	28·1	19·3
Aortic, with or without other valves	66·8	80·7
Aortic alone	1·4	10·9

In both diseases involvement of mitral and aortic is the most frequent combination, and in both the mitral is the most common single valve to be affected; but while in rheumatism the mitral is usually the first and more severely attacked, in endocarditis lenta the infection often appears to spread from the aortic valve to the mitral.

Now, in the cases with bicuspid aortic valves in which rheumatism or endocarditis lenta supervened, the aortic valve was *always* involved, contrary to the usual findings. This is particularly remarkable in rheumatism, where the aortic escapes more often than in endocarditis lenta, and it may be that the abnormality of the valve has in these cases made it more susceptible to the infection.

The incidence of secondary lesions of the aortic valve is summarized in Table E.

TABLE E.

Condition of Valves.	Number of Cases.
Gelatinous cushions on margin	4
Fibrous thickening	9
Atheroma	2
Calcareous nodules	4
Syphilitic endocarditis	2
Rheumatic endocarditis	5
Infective endocarditis	6
	32

Thus thirty-two of the fifty-two bicuspid valves were affected by secondary lesions; four of these, the gelatinous nodules, may have been part of the congenital malformation, the remainder were certainly acquired conditions.

The Association between the Bicuspid Valve and Endocarditis lenta.

With regard to the part played by the abnormality of the valve in the aetiology of endocarditis lenta, the following points may be noted:

(1) There were five cases of endocarditis lenta in this series, a number equal to the cases of rheumatic endocarditis, which is in general a more common disease. It is noteworthy, however, that these five cases all occurred during the period after 1918 when the disease became more common and was found particularly in ex-soldiers. At the London Hospital in the eight years 1911 to 1918 inclusive, thirty-eight cases came to necropsy, while in the same number of years, 1919 to 1926, there were sixty-four cases. The incidence of the bicuspid aortic valve, on the other hand, was greater in the earlier years, for thirty-five cases occurred in the seven years 1912 to 1918 and only seventeen in the eight years 1919 to 1926. This suggests that the malformation has only a partial influence in determining the infection.

(2) Lewis and Grant (3) concluded that '23 per cent. of all subjects possessing bicuspid valves acquire infective endocarditis after reaching adult life'. In this series thirty-seven were over twenty years old at death, and six of these died of infective endocarditis, a percentage of 16·2. Four of the six patients fought in France, and two had other congenital lesions, so that there were additional predisposing factors in five cases. (One of the ex-soldiers had constriction of the aorta and appears under both headings.)

(3) Looking at the subject from another point of view, Lewis and Grant (3) considered that at least a quarter of the cases of infective endocarditis, of the subacute or chronic type at any rate, were predisposed to the disease by a bicuspid condition of the aortic valve. At the London Hospital, during the period under review, necropsy was performed on ninety-five cases of endocarditis lenta, and in only five of these was a bicuspid valve found, i. e. in 5·3 per cent. The abnormality is, however, far more frequent in these patients than in unselected cases, being 1 in 19 compared with 1 in 267 (see p. 386), so that probably it in some way renders the patient more liable to this disease.

Age at Death.

The question arises whether the abnormality constitutes a handicap in the life of the subject in whom it occurs, and, although the number of patients is too small to draw conclusions, it is pertinent to consider their age at death so that these observations may be added to those of others.

The ages at death of the London Hospital patients are shown in Table F.

TABLE F.

Years	Under 5.	5 to 10.	10 to 20.	20 to 30.	30 to 40.	40 to 50.	50 to 60.	60 to 70.
Male	8	1	3	6	5	9	6	4
Female	1	0	2	0	3	1	0	3
Total	9	1	5	6	8	10	6	7

While 17·3 per cent. died under the age of five, less than half lived beyond forty, and none approached the span of threescore years and ten, the eldest being sixty-three when he died.

These figures agree with the ages at death in fifty cases collected from the literature:

Source.	No. of Cases.	No. under 5.	No. over 40.	Age of Eldest Patient.
Dilg (1)	19	6	3	68
Osler (4)	16	1	8	60
De Vries (2)	10	1	5	70
Babes (6)	5	0	1	40
	50	8	17	

Lewis and Grant (3) record that in 101 collected cases thirty-two patients were under twenty, and they give the ages of twenty-one who died under five; sixty-nine reached adult life.

TABLE G.

Cause of Death.	No. of Cases.		Case Numbers, Table III.
Endocarditis lenta	5		39, 42, 45, 47, 52
Acute infective endocarditis of aortic valve	1		38
Acute infective endocarditis of tricuspid valve	1		48
Acute rheumatic endocarditis	3		6, 33, 46
Chronic rheumatic endocarditis	1	14	31
Atheromatous endocarditis	1		43
Syphilitic endocarditis and aortitis	1		24
Congenital pulmonary stenosis	1		17
Peritonitis from various causes	8		2, 4, 11, 13, 14, 16, 27, 29
Broncho-pneumonia from various causes	8		3, 5, 7, 15, 18, 32, 35, 40
Accidents	5		9, 21, 23, 25, 51
Meningitis	3		10, 12, 30
Infections of the urinary tract	3		36, 37, 44
Septicaemia	1		49
Carcinoma of stomach	2		1, 41
Post-operative haemorrhage and shock	2		8, 28
Lobar pneumonia	1		34
Cirrhosis of the liver	1		19
Typhoid fever with empyema	1		20
Acute pleurisy and pericarditis	1		22
Epidemic gastro-enteritis	1		26
Death during anaesthesia	1		50
	52		

Cause of Death.

It has been shown that bicuspid valves are probably more liable than normal valves to degenerative and fibrotic processes and to infection by rheumatic, streptococcal, and other infections. How often have these conditions actually

killed the patient? Osler (4) said that in his eighteen cases death could be attributed to the anomaly in fifteen. An abstract of the causes of death in the London Hospital cases is presented in Table G (see also Table III).

Fourteen patients died from heart disease, but in three of these deaths the bicuspid aortic valve cannot be considered as an aetiological factor, viz. congenital pulmonary stenosis, acute tricuspid endocarditis, syphilitic endocarditis; subtracting these, 21·15 per cent. died from acquired cardiac lesions affecting the aortic valve and possibly facilitated by its abnormal structure. It is difficult to say how far aortic disease contributed to the death of the patient in other cases. For instance, in the death during anaesthesia and those from post-operative shock, it is possible that the abnormality of the valve may have impaired its function just enough to turn the scale, especially in the two cases where thickening of the cusps was found, and the same may be said of many of the infections. Of the five patients who died as the result of accidents, none showed signs of heart disease except 23 and 51, men of fifty-four years of age who had slight fibrotic conditions common at their time of life. Analysis of the sixteen cases of death from peritonitis and broncho-pneumonia shows that six followed perforation of a hollow viscus (2, 5, 14, 16, 27, 29), while one (7) was due to the entrance of a foreign body into the bronchus. These fatalities may perhaps be regarded as accidents in that they prevent our knowing the natural end to the patient's life, and on examining the hearts it is found that all but two (29 and 7) had chronic fibrotic conditions of the aortic valve, one rheumatic and the remainder degenerative. It is perhaps no more justifiable to consider death from the perforation of a gastric ulcer as accidental than death from septicaemia or any acute and overwhelming infection; nevertheless, it is interesting to note that, if these seven cases are deducted from the statistics, together with the five 'accidents', forty patients are left, of whom 27·5 per cent. died as the result of those acquired lesions to which the bicuspid valve is specially liable.

Summary.

1. The pathogenesis of variations from the normal number of cusps in the pulmonary and aortic valve is discussed, the conclusion being that these variations arise as errors in development.

2. In the case of the pulmonary valve it is submitted that such abnormalities are usually combined with more severe congenital lesions of the heart and do not by themselves predispose to acquired endocarditis.

3. Fifty-two cases of aortic bicuspid valve have been studied, particularly with reference to acquired lesions. In these cases fibrosis, atheroma and calcification of the aortic cusps, and rheumatic infection of the aortic valve were found rather more frequently than would be expected where the valve is normal, while infective aortic endocarditis occurred in 11·5 per cent. of the cases.

The causes of death in the fifty-two cases are analysed, and the evidence is

considered for believing that this minor abnormality of the aortic valve tends to render the patient more liable to disease, particularly to endocarditis lenta.

I am indebted to Professor Turnbull for permission to use the records of the Pathological Institute of the London Hospital.

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TABLE I.

Pulmonary Valve with Two Cusps.

1. Male, aged 4 days. **Other congenital abnormalities**: Patent ductus arteriosus; imperforate rectum; epispadias. **Acquired conditions of heart**: None. **Summary of necropsy**: Imperforate rectum; epispadias.

2. Male, aged 23 years. **Other congenital abnormalities**: Constriction 1 cm. below bases of pulmonary cusps (orifice = 0·3 cm. diameter). Absence of pars membranacea septi. **Acquired conditions of heart**: Rheumatic endocarditis of aortic, mitral, and tricuspid valves. **Summary of necropsy**: Melaena; erythraemia; acute and chronic rheumatic endocarditis; congenital malformation of heart; clubbing of fingers and stunted growth.

3. Male, aged 11 months. **Other congenital abnormalities**: Absence of central portion of median septum; hypoplasia of pulmonary commissure and pulmonary artery (each 2 cm. in circumference); ductus arteriosus patent. **Acquired conditions of heart**: None. **Summary of necropsy**: Heart failure; congenital malformation of heart.

4. Male, aged 54 years. **Other congenital abnormalities**: Partial fusion between anterior and left posterior aortic cusps; double inferior vena cava. **Acquired conditions of heart**: Slight fibrous thickening of aortic cusps, brown atrophy of heart. **Summary of necropsy**: Broncho-pneumonia, meningeal haemorrhage, laceration of brain (accident).

5. Male, aged 75 years. **Other congenital abnormalities**: Double ureter; diverticulum arising from second part of duodenum. **Acquired conditions of heart**: None. **Summary of necropsy**: Broncho-pneumonia following suprapubic prostatectomy.

Table II.

Pulmonary Valve with Four Cusps.

1. Male, aged 18 years. **Other congenital abnormalities**: None. **Acquired conditions of heart**: Chronic rheumatic endocarditis of mitral valve; infective endocarditis of mitral valve. **Summary of necropsy**: Subacute streptococcal endocarditis; chronic rheumatic endocarditis; acute and chronic pericarditis.

2. Female, aged 43 years. **Other congenital abnormalities**: Dilation of pulmonary artery (10 cm. in circumference); hypoplasia of left auricle and ventricle. **Acquired conditions of heart**: Fibrous thickening at margins of pulmonary valve; dilatation of right auricle and right ventricle. **Summary of necropsy**: Lobar pneumonia of lower lobe of right lung; chronic tuberculous cavity in upper lobe of right lung.

3. Male, aged 54 years. Small extra cusp between the two anterior pulmonary cusps. **Other congenital abnormalities**: None. **Acquired conditions of heart**: Slight concentric hypertrophy of left ventricle. **Summary of necropsy**: General fibrinous peritonitis; intestinal obstruction by fibrous adhesions (appendicectomy and drainage).

4. Female, aged 10 years. Small additional cusp ($0{\cdot}6 \times 0{\cdot}5$ cm.) between left anterior and posterior cusps. **Other congenital abnormalities**: Pulmonary stenosis **Acquired conditions of heart**: Slight hypertrophy of left ventricle (thickening and fusion of all cusps of pulmonary valve). **Summary of necropsy**: Haemoperitoneum; rupture of necrosed growth of coeliac glands; tubular carcinoma of right upper jaw (right ovarectomy two months previously at another hospital); congenital pulmonary stenosis.

Table III.

Aortic Valve with Two Cusps.

1. Female, aged 37 years. **Abnormality in aortic valve**: Imperfect separation of anterior and right posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Severe atheroma of aortic valves; calcareous nodules in both aortic cusps and in posterior cusp of mitral valve; brown atrophy of heart. **Summary of necropsy**: Marasmus; carcinoma of stomach; carcinomatosis of peritoneum.

2. Male, aged 42 years. **Abnormality in aortic valve**: Two cusps, one carrying the orifices of both coronary arteries. **Other congenital abnormalities**: None. **Associated heart lesions**: Thickening of margins of aortic and mitral cusps; slight hypertrophy of left ventricle. **Summary of necropsy**: General fibrino-purulent peritonitis; perforation of duodenal ulcer.

3. Male, aged 11 months. **Abnormality in aortic valve**: Fusion of anterior and right posterior cusps. **Other congenital abnormalities**: Ductus arteriosus patent; Meckel's diverticulum; amyotonia congenita. **Associated heart lesions**: Gelatinous cushions on contact margins of valves on either side of imperfect septum; dilatation of both ventricles. **Summary of necropsy**: Heart failure; broncho-pneumonia; amyotonia congenita.

4. Male, aged 63 years. **Abnormality in aortic valve**: Fusion of right and left posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Patches of subendocardial fat in both ventricles; calcareous patch on posterior aortic cusp in situation of absent septum. **Summary of necropsy**: General fibrino-purulent peritonitis; carcinoma of sigmoid colon (laparotomy).

5. Female, aged 34 years. **Abnormality in aortic valve**: Fused anterior and right posterior cusps with small septum. **Other congenital abnormalities**: None. **Associated heart lesions**: Thickening of fused cusps; simple atrophy of heart. **Summary of necropsy**: Broncho-pneumonia; subphrenic abscess; perforation of gastric ulcer (posterior gastro-jejunostomy).

6. Male, aged 6 years. **Abnormality in aortic valve**: Fusion of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Rheumatic endocarditis of aortic and mitral valves. **Summary of necropsy**: Heart failure; acute and chronic rheumatic endocarditis.

7. Male, aged 1 year. **Abnormality in aortic valve**: Partial separation of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: None. **Summary of necropsy**: Broncho-pneumonia; foreign body in left bronchus (tracheotomy).

8. Male, aged 26 years. **Abnormality in aortic valve**: Two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Thickening of contact margin, and nodule of atheromatous thickening at base of aortic cusps. **Summary of necropsy**: Haemoperitoneum (splenectomy); island cirrhosis of liver.

9. Male, aged 36 years. **Abnormality in aortic valve**: Fusion of the cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: None. **Summary of necropsy**: Accident, fractured skull (trephining); syphilitic aortitis.

10. Male, aged 8 months. **Abnormality in aortic valve**: Fusion of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: None. **Summary of necropsy**: Purulent meningitis (mastoidectomy).

11. Male, aged 14 years. **Abnormality in aortic valve**: Incomplete separation of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Atheromatous thickening at base of mitral valve. **Summary of necropsy**: General fibrino-purulent peritonitis (appendicectomy).

12. Male, aged 51 years. **Abnormality in aortic valve**: Fusion of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Fatty and calcareous plaques at bases of mitral and aortic cusps. **Summary of necropsy**: Purulent basal meningitis; abscess of brain (pneumococcal); pneumonia and bronchiectasis.

13. Male, aged 62 years. **Abnormality in aortic valve**: Fusion of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Simple atrophy of heart; fatty plaques at bases of mitral and aortic cusps. **Summary of necropsy**: General faecal peritonitis (ileo-colostomy for carcinoma of caecum).

14. Female, aged 62 years. **Abnormality in aortic valve**: Fusion of two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Fatty and calcareous plaques at bases of mitral and aortic valves; adiposity of myocardium. **Summary of necropsy**: General purulent peritonitis; stricture of rectum and colon; perforation of sigmoid colon (colostomy).

15. Female, aged 1 year 8 months. **Abnormality in aortic valve**: Fusion of two cusps. **Other congenital abnormalities**: Hypoplasia of cortex and medulla in lower pole of left kidney; pouching round orifices of ureters in urinary bladder; double opening to right ureter. **Associated heart lesions**: None. **Summary of necropsy**: Broncho-pneumonia.

16. Male, aged 42 years. **Abnormality in aortic valve**: Small septum between right and left posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Chronic rheumatic endocarditis of aortic valve. **Summary of necropsy**: General fibrino-purulent peritonitis; perforation of jejunal ulcer.

17. Male, aged 1 year. **Abnormality in aortic valve**: Two cusps. **Other congenital abnormalities**: Pulmonary stenosis (orifice = 0·13 cm. in diameter). **Associated heart lesions**: Thickening and retraction of tricuspid valve with minute varicosity on septal cusp; hypertrophy of right ventricle and of right auricle. **Summary of necropsy**: Heart failure; congenital morbus cordis; stenosis of pulmonary valve.

18. Male, aged 55 years. **Abnormality in aortic valve**: Imperfect differentiation of anterior and right posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Large calcareous nodules in aortic cusps. **Summary of necropsy**: Broncho-pneumonia; abscess of lung; carcinoma of oesophagus invading right lung and pericardium.

19. Male, aged 22 years. **Abnormality in aortic valve:** Imperfect separation of anterior and right posterior cusps. **Other congenital abnormalities:** None. **Associated heart lesions:** Thickening of fused cusps; simple atrophy of heart. **Summary of necropsy:** Cirrhosis of liver.

20. Male, aged 37 years. **Abnormality in aortic valve:** Imperfect division of one cusp into anterior and right posterior cusps. **Other congenital abnormalities:** None. **Associated heart lesions:** Slight thickening of free margin of imperfectly divided cusp. **Summary of necropsy:** Typhoid fever; organizing pericarditis; interlobar empyema (resection of rib).

21. Male, aged 1 year 11 months. **Abnormality in aortic valve:** Imperfect separation of anterior from right posterior cusp. **Other congenital abnormalities:** None. **Associated heart lesions:** None. **Summary of necropsy:** Haemoperitoneum; haemopleura; rupture of lungs and liver; fractured ribs (accident: run over).

22. Male, aged 56 years. **Abnormality in aortic valve:** Partial separation of left and right posterior cusps. **Other congenital abnormalities:** None. **Associated heart lesions:** Concentric hypertrophy of left ventricle. **Summary of necropsy:** Acute sero-fibrinous pleurisy and pericarditis; cardiovascular hypertrophy; chronic interstitial nephritis.

23. Male, aged 54 years. **Abnormality in aortic valve:** Ill-defined septum between anterior and right posterior cusps. **Other congenital abnormalities:** Fenestration of left posterior aortic cusp, near its free edge; Meckel's diverticulum. **Associated heart lesions:** Patch of fibrosis in endocardium of right ventricle. **Summary of necropsy:** Anaemia from haemorrhage; laceration of left arm, left leg, and right foot (accident); amputation of lacerated leg.

24. Male, aged 49 years. **Abnormality in aortic valve:** Two cusps, one anterior, one posterior. **Other congenital abnormalities:** None. **Associated heart lesions:** Partial myocardial infarction; syphilitic endocarditis of aortic valve; hypertrophy of heart, especially of left ventricle. **Summary of necropsy:** Heart failure; syphilitic aortic endocarditis; infarction and fibrosis of myocardium; stenosis of left coronary orifice; syphilitic aortitis.

25. Male, aged 51 years. Partial separation of anterior and left posterior cusp. **Other congenital abnormalities:** None. **Associated heart lesions:** None. **Summary of necropsy:** Extreme anaemia; laceration of legs, &c. (railway accident); fat embolism.

26. Male, aged 1 year 7 months. **Abnormality in aortic valve:** Incomplete separation of anterior and right posterior cusps, and to a lesser degree of anterior and left posterior. **Other congenital abnormalities:** None. **Associated heart lesions:** Cushion-like thickening at junctions of imperfectly separated cusps. **Summary of necropsy:** Gastro-enteritis (summer diarrhoea).

27. Male, aged 41 years. **Abnormality in aortic valve:** Incomplete separation between anterior and left posterior cusps. **Other congenital abnormalities:** None. **Associated heart lesions:** Fibrotic thickening; nodular calcification and distortion of aortic cusps. **Summary of necropsy:** General peritonitis; perforation of small intestine (reduction of volvulus).

28. Female, aged 42 years. **Abnormality in aortic valve:** Partial differentiation between anterior and right posterior cusps. **Other congenital abnormalities:** None. **Associated heart lesions:** None. **Summary of necropsy:** Heart failure after operation for removal of pituitary neoplasm.

29. Male, aged 37 years. **Abnormality in aortic valve:** Imperfect differentiation between anterior and left posterior cusps. **Other congenital abnormalities:** None. **Associated heart lesions:** None. **Summary of necropsy:** Septicaemia; general fibrinous peritonitis; perforation of duodenal ulcer (gastro-jejunostomy).

30. Male, aged 14 years. **Abnormality in aortic valve:** Two cusps, equal in size, one composed of poorly differentiated anterior and left posterior cusps. **Other congenital abnormalities:** Horseshoe kidney containing cysts. **Associated heart lesions:** None. **Summary of necropsy:** Tuberculous meningitis; partially disseminated tuberculosis.

31. Male, aged 45 years. **Abnormality in aortic valve**: Two cusps, one anterior, one posterior. **Other congenital abnormalities**: None. **Associated heart lesions**: Hypertrophy of ventricles (considerable) and of left auricle (slight); calcareous nodules in aortic cusps; fibrous thickening of endocardium; rheumatic endocarditis of aortic and less of mitral valve. **Summary of necropsy**: Heart failure; aortic stenosis; rheumatic endocarditis.

32. Male, aged 27 years. **Abnormality in aortic valve**: Two cusps with septum between. **Other congenital abnormalities**: None. **Associated heart lesions**: Fibrous thickening of septum and of adjacent parts of cusps. **Summary of necropsy**: Septicaemia; acute pleurisy and broncho-pneumonia.

33. Male, aged 12 years. **Abnormality in aortic valve**: Fusion of anterior and left posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Pouch in right margin of right posterior cusp; rheumatic endocarditis of mitral and aortic valves. **Summary of necropsy**: Heart failure; rheumatic endocarditis.

34. Male, aged 49 years. **Abnormality in aortic valve**: Two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Recent infarction of myocardium of left ventricle; hypertrophy of heart; syphilitic aortic endocarditis. **Summary of necropsy**: Lobar pneumonia; aortic incompetence; syphilitic aortic endocarditis and aortitis.

35. Male, aged 61 years. **Abnormality in aortic valve**: Two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: None. **Summary of necropsy**: Aspiration broncho-pneumonia; general fibrino-purulent peritonitis (appendicectomy), erythraemia.

36. Male, aged 60 years. **Abnormality in aortic valve**: Imperfect differentiation between anterior and left posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Thickening of free margin of fused cusps and of left half of right posterior aortic cusp. **Summary of necropsy**: Oedema of lungs; haemorrhagic cystitis; enlarged prostate; urethral stricture (suprapubic cystotomy).

37. Male, aged 4 years. **Abnormality in aortic valve**: Imperfectly separated anterior and left posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Cushion-like thickening of free margins of fused aortic cusps; hypertrophy of left ventricle. **Summary of necropsy**: Heart failure; cardiac hypertrophy; chronic bilateral streptococcal pyonephrosis.

38. Male, aged 34 years. **Abnormality in aortic valve**: Two cusps, one right and one left. **Other congenital abnormalities**: None. **Associated heart lesions**: Infective (streptococcal) endocarditis of aortic valve. **Summary of necropsy**: Acute and subacute nephritis; streptococcal septicaemia; acute infective endocarditis.

39. Male, aged 28 years. **Abnormality in aortic valve**: Imperfect differentiation between anterior and right posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Infective endocarditis of aortic valve. **Summary of necropsy**: Heart failure; aortic incompetence; chronic infective endocarditis.

40. Male, aged 40 years. **Abnormality in aortic valve**: Slight adhesions between cusps. **Other congenital abnormalities**: Fenestration of aortic cusps. **Associated heart lesions**: None. **Summary of necropsy**: Broncho-pneumonia; medullary carcinoma of bronchus with secondaries in mediastinal glands.

41. Female, aged 61 years. **Abnormality in aortic valve**: Adhesions between adjacent margins of cusps. **Other congenital abnormalities**: Fenestration of aortic cusps. **Associated heart lesions**: Adiposity of myocardium of right ventricle. **Summary of necropsy**: Heart failure; anaemia; carcinoma of stomach (gastro-jejunostomy).

42. Male, aged 41 years. **Abnormality in aortic valve**: Ill-defined demarcation between anterior and left posterior cusps. **Other congenital abnormalities**: Constriction of aorta (5 cm. circumference) at site of obliterated ductus arteriosus. **Associated heart lesions**: Infective endocarditis of aortic valve spreading to aortic cusps of mitral valve. **Summary of necropsy**: Heart failure; subacute bacteriaemic endocarditis.

43. Female, aged 62 years. **Abnormality of aortic valve**: Two cusps, one corresponding to each coronary artery. **Other congenital abnormalities**: None. **Associated heart lesions**: Calcareous nodules in right aortic cusp; atheromatous vegetations and fibrosis of left cusp; fibrous thickening of posterior cusp of mitral valve; hypertrophy of left auricle. **Summary of necropsy**: Heart failure; aortic stenosis; chronic atheromatous endocarditis of aortic valve.

44. Male, aged 32 years. **Abnormality of aortic valve**: Two cusps, one with indistinct division into two, opposite right coronary orifice. **Other congenital abnormalities**: None. **Associated heart lesions**: Thickening of free margin of aortic cusps; slight relative hypertrophy of left ventricle. **Summary of necropsy**: Ascending nephritis; sero-pyonephrosis; cystitis; angioma upon filum terminale within cauda equina.

45. Female, aged 32 years. **Abnormality of aortic valve**: Two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Infective endocarditis of aortic valve spreading to aortic cusp of mitral valve. **Summary of necropsy**: Bacteriaemia; subacute fibrino-purulent aortic endocarditis.

46. Female, aged 16 years. **Abnormality of aortic valve**: Two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Rheumatic endocarditis of mitral and less of aortic valve. **Summary of necropsy**: Broncho-pneumonia; influenza; acute rheumatic endocarditis.

47. Male, aged 25 years. **Abnormality of aortic valve**: Two cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Infective endocarditis of aortic valve and aortic cusp of mitral valve. **Summary of necropsy**: Subacute streptococcal endocarditis.

48. Female, aged 19 years. **Abnormality of aortic valve**: Septum between anterior and left posterior cusps represented by a ridge. **Other congenital abnormalities**: Orifice (0·4 cm. diameter) in interventricular septum below pars membranacea septi. **Associated heart lesions**: Infective endocarditis of tricuspid valve and mural endocardium. **Summary of necropsy**: Pulmonary infarcts and abscesses; pyaemia; acute pneumococcal tricuspid endocarditis.

49. Male, aged 4 months. **Abnormality of aortic valve**: Two cusps, one anterior, one posterior; origin of both coronaries from sinus of anterior cusp. **Other congenital abnormalities**: None. **Associated heart lesions**: Gelatinous cushions in free margins of aortic cusps; hypertrophy of left ventricle. **Summary of necropsy**: Septicaemia (no primary focus found).

50. Male, aged 47 years. **Abnormality of aortic valve**: Fibrous union between margins of anterior and right posterior cusps. **Other congenital abnormalities**: None. **Associated heart lesions**: Slight thickening of margin of left posterior aortic cusp. **Summary of necropsy**: Death during anaesthesia for operation on semilunar cartilage.

51. Male, aged 54 years. **Abnormality of aortic valve**: Partial fusion between anterior and left posterior cusps. **Other congenital abnormalities**: Two transparent cusps in pulmonary valve; double inferior vena cava joining above at site of left renal vein. **Associated heart lesions**: Slight fibrous thickening of aortic cusps; brown atrophy of heart. **Summary of necropsy**: Broncho-pneumonia; meningeal haemorrhage; laceration of brain (accident).

52. Male, aged 23 years. **Abnormality of aortic valve**: Fusion of anterior and left posterior cusps. **Other congenital abnormalities**: Orifice in interventricular septum; constriction at upper part of descending thoracic aorta just admitting a probe; enlargement of subclavian arteries, &c. **Associated heart lesions**: Infective endocarditis of both aortic cusps, aortic cusp of mitral, posterior pulmonary cusp and orifice in interventricular septum. **Summary of necropsy**: Aortic incompetence; subacute streptococcal endocarditis; congenital malformation of heart; coarctation of aorta.

CREATINE AND RIGIDITY[1]

By MARION HIRST and C. G. IMRIE
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Historical.

It has always been difficult to believe that creatine, the principal nitrogenous substance other than protein in voluntary muscles, has nothing to do with their functions. It is found in many other organs, but only in much smaller concentration; in the heart as also in the testis about half, in the brain about a quarter of the amount in striated muscle, in the smooth muscle less than in the brain, and in the other organs less still. It is also difficult to believe that the creatinine in the urine, again the principal nitrogenous substance in it apart from urea, has nothing to do with the creatine of the body, of which it is merely an internal anhydride, and into which, in the laboratory at least, it is so easily converted. Proof, however, that this conversion is effected also in the body has been slow in coming to light, and since Folin showed that creatine taken in the food, in the doses which he used, caused no increase in the creatinine of the urine, while some of that which had been taken was excreted unchanged, it was for many years common to interpret this lack of proof as amounting to proof that the change did not occur and that therefore the creatinine in the urine had no relation to the creatine in the body; and since the creatine in a man's muscles amounts to 100 grm. or so, and in all the rest of his body to not more than 2 or 3 grm., this interpretation implied that the creatinine in the urine had no relation to muscular functions.

It was, however, shown long ago by Leathes (1, 2) that the rate of creatinine output was about 25 per cent. higher by day than by night, and that this rate was increased 25 per cent. by vigorous exercise. It was also shown that the voluntary maintenance of the muscles in a state of tonic contraction increased the output of creatinine (3); that the amount of creatine in frog's muscle was increased by prolonged activity (4) and particularly was increased in the clasping muscles during the breeding season (5); that the amount of creatinine excreted, which in any one subject is fairly constant, is roughly proportional to the development of his muscular system, and that in certain abnormal conditions of the muscles, myotonia congenita and the muscular dystrophies, creatine appears in the urine.

[1] Received November 16, 1927.

It would not have been difficult, however, to assemble evidence as conclusive as this or hardly more inconclusive for the dissociation of urinary creatinine and even creatine from any relation to muscular functions, until 1927, when there appeared the accounts by Fiske and Subbarrow (6) and by P. and G. P. Eggleton (7) of their remarkable independent discoveries. Fiske and Subbarrow found an unstable compound containing phosphoric acid and creatine in perfectly fresh excised cat's muscle which very soon begins to disappear, and in a few hours after removal is no longer present, while in proportion as it disappears free phosphoric acid and creatine in molecular ratio to one another appear in its place. Since stimulation diminishes the amount of this unstable compound and stimulation during arrest of the circulation through the muscle causes it to break up completely, and since, if, even in the latter case with the blood-supply restored, the muscle be allowed to rest, the combination of phosphoric acid with creatine proceeds afresh, and at the end of an hour is found in considerable amount, they rightly can claim that creatine now has an obvious bearing on the mechanism of muscular contraction.

Essentially the same results were obtained with frog's muscle by P. and G. P. Eggleton, who, however, have published a fuller account of their work, confirming the presence in similar conditions of the labile compound of phosphoric acid which they call phosphogen, though without, at the time of publication, having identified the presence of creatine in it.

Creatinuria in Post-encephalitic Rigidity.

The observation that creatinuria occurs in patients who develop muscular (Parkinsonian) rigidity as a sequela of epidemic encephalitis suggested that additional data as to the relation between creatinine, creatine, and disorders of the voluntary muscles should be looked for by studying this form of creatinuria. The methods which were used for estimating the amount of the different nitrogenous substances in the urine were the same as in the previous work (Hirst and Imrie, 8). The diets employed, except where otherwise stated, contained no creatine, creatinine, or purine derivatives.

First of all, in order to confirm the fact of the general occurrence of creatinuria in post-encephalitic rigidity, samples of urine were obtained from 12 subjects attending at the 'encephalitis' out-patient clinic of Professor Arthur Hall. The cases exhibited a marked degree of rigidity. In every instance the urine contained creatine. The patients were on their ordinary diets and the urine was voided at the clinic. In the female cases the urine was obtained several days after the last menstrual period.

The creatine and creatinine were determined and the results, expressed in milligrams per 100 c.c., are set out in Table I. The specific gravity of the urines varied considerably, so the figures give no indication of the amount eliminated in 24 hours. They establish, however, the existence of the creatinuria. In addition, the figures for the nitrogen excreted as creatine, expressed as a fraction

of the nitrogen eliminated as creatine and creatinine together, are included. There is a tendency for this ratio to be higher in the females than in the males, an average of 16·6 per cent. in the former as compared with 10·4 per cent. in the latter.

TABLE I.

Females.	Creatinine.	Creatine.	Nitrogen as Creatine / N. as Creatine + Creatinine.
			%.
1	50·5	10·9	15·68
2	166·7	61·9	24·20
3	23·5	3·6	11·66
4	40·6	6·61	12·28
5	23·2	4·17	13·42
Males.			
1	52	12·9	17·42
2	93	14·1	11·57
3	80	12·18	11·60
4	93·5	12·3	10·20
5	219	28·0	9·86
6	110	9·75	7·10
7	82	5·34	5·32

Figures for creatine and creatinine are expressed as milligrams per 100 c.c. of urine.

In the paper previously referred to (8) tables are published giving data as to the nitrogenous constituents of the urine from four cases of rigidity who were on a constant diet and observed over a considerable period of time. The 24 hours were divided into four periods, 7 a.m. to 12 noon, 12 noon to 5 p.m., 5 p.m. to 9 p.m., and 9 p.m. to 7 a.m. The complete tables need not be reproduced here, but the average figures for the creatine and creatinine are included in Table II.

It should be noted that:

1. The amount of creatine and creatinine excreted per hour is greater by day than by night, as was found to be the case for creatinine in normal subjects by Leathes (1) and for creatine in children by Raper.

2. The amount of creatine excreted by the three males varies directly with the degree of rigidity. Case II, least rigid, never excreted any at night and sometimes none at certain periods of the day. Case IV, most rigid, excreted most, especially in proportion to his body-weight; thus expressed, his output was almost four times that of Case II.

3. The amount of creatinine in proportion to the body-weight is also greatest in the most rigid case.

4. The amount of uric acid, similarly, is also greatest in the most rigid case.

Case III, female, moderately rigid, must be considered separately. Creatine is not uncommonly present in the urine of normal females, though not in the amount found here, 4·6 mg. per kg. of body-weight, which is higher than the average for the last days of pregnancy, when the output is normally high. The figures given here were obtained several days after the last menstrual period. In proportion to the body-weight the output is greater than in the most rigid male subject. The nitrogen as creatine, expressed as a fraction of the nitrogen as

TABLE II.

Case.	No. of Days.	7 a.m.–12 n.		12 n.–5 p.m.		5 p.m.–9 p.m.		9 p.m.–7 a.m.		Total in 24 hours.		Mg. per Kg. Body-weight.		Mg. per Kg. Body-weight.	Rigidity.
		Creatine.	Creatinine.	Creatine.	Creatinine.	Creatine.	Creatinine.	Creatine.	Creatinine.	Creatine.	Creatinine.	Creatine.	Creatinine.	Uric Acid.	
											Grm.				
2 ♂	5	2·9	62·2	3·9	60·6	3·8	55·2	0	49·2	50·0	1·33	0·7	18·75	4·96	+
5 ♂	10	4·6	58·3	5·3	65·2	3·2	58·0	1·9	44·6	80·4	1·34	1·37	22·90	6·83	+ +
4 ♂	3	5·0	65·5	4·9	53·5	6·6	56·5	3·1	52·6	107·0	1·35	2·70	26·50	9·20	+ + +
3 ♀	8	12·0	35·7	9·2	40·2	10·2	33·8	6·9	36·0	215·0	0·89	4·57	18·92	5·66	+ +

(1) During the periods the figures are expressed as milligrams per hour.
(2) Figures for the 24-hourly output express creatine in milligrams and creatinine in grammes.

TABLE III.

Case V. Experiment I.					*Case IV. Experiment II.*					Normal Subject calculated from Rose and Dimmitt's Figures.		
Date.	Dose of Creatine.	Creatine.	Creatinine.	Urine.	Date.	Dose of Creatine.	Creatine.	Creatinine.	Urine.	Dose of Creatine.	Creatine.	Creatinine.
July 14–20. Average.	—	0·069	1·276	588	July 11–20. Average.	—	0·07	1·238	900	—	—	1·35
21	0·9	0·056	1·367	1123	21	0·9	0·081	1·198	1401	1	0·09	1·45
22	1·8	0·299	1·289	1187	22	1·8	0·225	1·179	854	2	0·130	1·51
23	4·5	0·620	1·260	1030	23	4·5	1·628	1·225	1121	5	1·810	1·59
24	9·0	4·170	1·369	861	24	9·0	3·950	1·379	1205	10	5·810	1·61
25	—	0·231	1·290	823	25	—	0·146	1·302	886			
26	—	0·085	1·350	757	26	—	0·078	1·287	862			

Creatine and creatinine expressed in grammes, urine in c.c.

creatine and creatinine together, is 17·3 per cent., which is a little higher than the average of the similar ratios obtained from the female cases recorded in Table I. This form of muscular rigidity, then, is associated with the excretion of creatine in females as well as in males.

Creatinine is commonly excreted in smaller amounts by females than males. But in this case of rigidity the amount is high; in proportion to the body-weight, as high as in Case II, who, however, is not so rigid.

The explanation of creatinuria in the different conditions in which it occurs has not been given. But its association with Parkinsonian rigidity may call to mind the fact that the amount of creatine in the clasping muscles of the frog is increased during the time when their function is active (5). This suggests, as a possible explanation of creatinuria in the conditions here studied, that the rigid muscles here also contain an increased amount of creatine.

Now it has been shown that it is possible to increase the creatine content of the muscles experimentally. When creatine is taken by mouth some of it appears to be retained in the body, and the muscles are found to contain more than before. Folin and Denis (9) on one occasion found the creatine in the muscles of a cat to be increased 26 per cent. during the absorption of creatine from the intestine. If now, in Parkinsonian rigidity, the amount of creatine in the muscles is increased and this increase accounts for the creatinuria, it is pertinent to inquire what will happen if the attempt is made to increase the amount in the muscles still further by the administration of creatine by mouth. If the muscles, the organs that contain perhaps as much as 98 per cent. of the creatine in the body, contain more in this condition than is normal, then it might be expected that they would be less able than normally to take up more creatine and a larger proportion of that taken by mouth would be excreted.

Experiments.

Experiments were carried out on three subjects, two males and one female. They were placed upon a diet containing no creatine, creatinine, or purine derivatives for at least five days before the administration of creatine. In some instances the urine was collected for periods of 24 hours, in others for four periods daily ending at 7 a.m., noon, 5 p.m., and 9 p.m.

Experiment I, male, W., 58·6 kg. (Case V of the series previously published). The creatine and creatinine in the urine were determined seven days before the creatine was given, and then on four successive days, at 9 a.m., four increasing doses, 0·9, 1·8, 4·5, and 9 grm., of creatine dissolved in warm water were given. The results are shown in Table III, Case V.

It is seen that the dose of 0·9 grm. of creatine causes no increase in the creatinuria of this subject, but larger doses do so progressively up to an output of more than 4 grm. after the largest dose of 9 grm. On the second day following this dose the output is still somewhat high, but on the third day it has returned almost to the normal value for this subject. The total additional

TABLE IV.

Date.	Dose of Creatine.	9 p.m.–7 a.m. Crea-tine.	9 p.m.–7 a.m. Crea-tinine.	9 p.m.–7 a.m. Urine.	7 a.m.–12 noon. Crea-tine.	7 a.m.–12 noon. Crea-tinine.	7 a.m.–12 noon. Urine.	12 noon–5 p.m. Crea-tine.	12 noon–5 p.m. Crea-tinine.	12 noon–5 p.m. Urine.	5–9 p.m. Crea-tine.	5–9 p.m. Crea-tinine.	5–9 p.m. Urine.	Total in 24 hours. Crea-tine.	Total in 24 hours. Crea-tinine.	Total in 24 hours. Urine.
Case V. Exp. III.																
July																
26	—	—	—	—	—	—	—	—	—	—	—	—	—	0·085	1·350	757
27	1·8	0·238	0·515	188	0·027	0·143	197	0·049	0·417	428	0·206	0·303	227	0·339	1·378	1040
28	4·5	1·078	0·660	430	0·145	0·264	271	0·045	0·328	201	0·018	0·244	122	1·286	1·496	1020
29	9·0	2·450	0·574	220	0·417	0·330	172	0·115	0·320	146	0·036	0·280	98	3·010	1·517	636
30	18·0	4·04	0·696	299	1·295	0·389	268	0·406	0·376	156	0·100	0·186	60	5·84	1·647	783
31	—	—	—	—	—	—	—	—	—	—	—	—	—	0·310	1·535	402
Average for 4 following days		—	—	—	—	—	—	—	—	—	—	—	—	0·123	1·395	697
3 days later		—	—	—	—	—	—	—	—	—	—	—	—	0·156	1·498	819
Case IV. Exp. IV.																
July	Grm.															
26	—	—	—	—	—	—	—	—	—	—	—	—	—	0·078	1·287	862
27	1·8	0·306	0·514	243	0·018	0·196	390	0·016	0·399	413	0·002	0·237	199	0·343	1·346	1245
28	4·5	1·140	0·580	495	0·146	0·311	429	0·015	0·297	210	0·026	0·225	111	1·327	1·414	1245
29	9·0	3·070	0·657	305	0·154	0·343	451	0·014	0·348	262	0·025	0·251	134	3·262	1·598	1152
30	18·0	5·290	0·767	391	0·820	0·359	238	0·063	0·106	59	0·166	0·489	188	6·338	1·720	876
Average for 5 following days		—	—	—	—	—	—	—	—	—	—	—	—	0·128	1·654	747
6 days later		—	—	—	—	—	—	—	—	—	—	—	—	0·061	1·299	900

Figures express creatine and creatinine in grammes, urine in c.c.

output for the six days following the first dose amounts to about 5 grm.; 16·2 grm. having been taken in all.

The creatinine output is somewhat irregular, but it appears that the urine contained about a quarter of a gramme more than it would otherwise have done, and if this was formed from the creatine administered, it corresponds to about 0·3 grm. of creatine, so that after taking 16·2 grm. about 5·3 grm. may be accounted for in these ways.

Experiment II, male, H., 52 kg., markedly rigid (Case IV of the series previously published).

Conditions of experiment similar to those in Experiment I.

The results are recorded also in Table III.

The creatine excretion is similar to that observed in Experiment I, except that rather more creatine was excreted after the third dose (4·5 grm.), rather less after the fourth (9 grm.). The additional output of creatine, amounting in six days to about 5·7 grm., which, with the additional creatinine (about 0·15 grm.) that appears to result from the administration of 16·2 grm., accounts for nearly 6 grm.

The results obtained in these two cases are therefore very similar. A considerable amount of creatine appears to be retained by both these rigid subjects, in fact rather more than by two normal subjects. When in Rose and Dimmitt's experiment (10) one of these subjects (R.) had received 18 grm. of creatine in doses of 1, 2, 5, and 10 grm., as is shown in Table III, it was possible to account for almost 8 grm., about 44 per cent., in the urine as compared with 5 and 6 grm. recovered from 16·2 grm., or about 31 and 37 per cent. in the two experiments reported here. Expressed as a fraction of the body-weight, the creatine which appears to be retained amounts to 191 mg. and 202 mg. per kg. in the rigid subjects, and 142 mg. in the normal one.

The difference is more marked when still larger doses of creatine are given. In Experiment III (Table IV, Case V) on the same subject as in Experiment I, the urine was collected four times during the day as shown in Table IV, where the results of giving four doses of creatine, amounting in all to 33·3 grm., are set out. There was an interval of three days between the beginning of this experiment and the end of Experiment I. It will be seen that a large proportion of the creatine appears to be retained, and a definite increase in the output of creatinine occurs.

Here again figures obtained by Rose and Dimmitt (10, p. 350) with somewhat similar doses from a normal subject are available for comparison. On the day after the largest dose that they gave (20 grm.), more than 15 grm. were recovered in the urine; in our experiment with the rigid man after 18 grm., the amount of creatine recovered was less than 6 grm.: in theirs the total amount recovered after three doses totalling 35 grm. came to about 16·5 grm.; in ours after 33 grm. it was 10·5 grm. It is of importance to note that our rigid subject weighed 12·3 kg. less than the normal one. The normal subject apparently retained 225 mg. per kg. of body-weight, the rigid case 432 mg.

TABLE V.

Case III.

Creatine at 12 noon.		12 noon–5 p.m.			5 p.m.–9 p.m.			9 p.m.–7 a.m.			7 a.m.–12 noon.			Total in 24 hours.		
Date.	Dose of Creatine.	Creatine.	Creatinine.	Urine.	Creatine.	Creatinine.	Urine.	Creatine.	Creatinine.	Urine.	Creatine.	Creatinine.	Urine.	Creatine.	Creatinine.	Urine.
Average for 6 normal days		—	—	—	—	—	—	—	—	—	—	—	—	0·123	0·854	1406
August																
4	0·9	0·300	0·192	339	0·146	0·151	336	0·035	0·415	544	0·136	0·350	536	0·617	1·108	1755
5	1·8	0·700	0·184	258	0·350	0·185	138	0·346	0·366	183	0·105	0·185	372	1·502	0·920	951
6	4·5	2·075	0·240	449	0·470	0·187	277	0·315	0·363	167	0·173	0·393	425	3·035	1·184	1318
7	9·0	1·820	0·243	172	0·567	0·143	240	0·895	0·501	333	0·290	0·187	189	3·572	1·074	934
8	18·0	6·300	0·282	457	1·270	0·355	379	1·793	0·460	372	0·285	0·195	516	9·648	1·291	1724
9	—	0·306	0·225	158	0·222	0·216	112	[0·071	0·083	57]	0·136	0·188	417	[0·735	0·712	744]
10	—	0·156	0·228	167	0·111	0·158	197	0·217	0·400	160	0·084	0·168	367	0·568	0·954	891

Creatine and creatinine expressed in grammes, urine in c.c. [ ] specimen of urine incomplete.

Two additional points for comment appear in this experiment. Twenty years ago, Folin had found that creatine given in small amounts appeared in part unchanged in the urine, but caused no increase in the output of creatinine. On this observation rested the belief that the urinary creatinine was not derived from the muscle creatine, and arose by metabolic processes that were not connected with creatine at all. Using the larger doses that were also used in our experiments and in others to be described, Rose and Dimmitt found that the creatinine output was increased. This is seen to occur in our rigid subjects and to about the same extent as in the normal ones. Their results, which we thus confirm, removed the difficulty which Folin's results had raised and made it possible to look, as the natural tendency had always been, to the creatine in the body, much the largest part of which is in the muscles, for the source of the creatinine in the urine.

From the separation of each day's urine into four periods, it is possible to follow the course of excretion throughout the 24 hours following each dose, which in this experiment was given at 9 p.m. Much the larger part comes out in the first ten hours—that is, during the night in this case; in the other three periods before the next dose the amount excreted diminishes rapidly. This indicates that the lower output of creatine that is commonly found at night is not due to nocturnal diminution of the power of the kidney to excrete, but to actual diminution of production during the night.

Experiment IV, in the same subject as Experiment II, namely Case IV, is set out also in Table IV, and is similar to it in all respects. The total creatine recovered from the urine amounts to 11·27 grm., as compared with 10·47 grm. in Experiment III; most of it appears in the first ten hours. The creatinine is definitely increased, and after the largest dose is 33 per cent. higher than on the days before creatine was given.

Experiment V, of a similar nature, was carried out on the female subject, Case III, who is amongst those reported in Table II and noted above as a case of marked rigidity with a higher degree of creatinuria than can fairly be accounted for by the mere fact that she was a woman. Five increasing doses of creatine, 0·9, 1·8, 4·5, 9, and 18 grm., that is 34 grm. in all, were given on five successive days in this experiment at noon instead of 9 p.m. On one occasion, from 9 p.m. to 7 a.m. on August 9, the day after the last dose, some of the urine was lost, as can be seen from Table V.

The figures given in the table show that this patient, who was excreting more creatine than male patients before being given creatine, excreted much more of that which was administered, even after smaller doses. Allowing for the last specimen on the day after the last dose, practically 19 grm. of extra creatine were excreted out of the 34·2 administered. If this means that she retained 15·2 grm. out of the 34·2 grm., then the men retained about 22 grm. out of the 34·2 grm. given. Moreover, the rate of elimination appears to have been higher; more was excreted in the five hours following the administration than in the nine-hour period following the same doses taken by the men. At the same time the

TABLE VI.

Case IV. Experiment VI.

Date.	Total Nitrogen.		Urea.		Uric Acid.		Creatinine.		Creatine.		Nitrogen as Ammonia.		Urine.		Total in 24 Hours. Total Nitrogen.	Urea.	Uric Acid.	Creatinine	Creatine.	Nitrogen as Ammonia.	Urine.	
Sept.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.								
27	5·39	6·95	—	—	0·154	0·158	0·521	0·669	0·013	0·056	0·257	0·395	938	763	12·34	—	0·312	1·19	0·069	0·652	1701	
28	5·17	6·90	—	—	0·121	0·180	0·486	0·712	0·029	0·041	0·240	0·352	693	453	12·07	—	0·301	1·20	0·071	0·592	1146	
29	7·04	5·0	—	—	0·274	0·131	0·742	0·474	0·050	0·040	0·325	0·260	650	276	12·04	—	0·405	1·22	0·09	0·585	926	
Oct. 4	12·0	5·61	—	—	0·440	0·167	1·087	0·747	7·52	0·215	0·325	0·279	574	246	17·61	—	0·607	1·83	7·735	0·604	820	Creatine 18 grm.
5	6·12	6·39	—	—	0·222	0·198	0·673	0·758	0·052	0·058	0·247	0·289	298	284	12·50	—	0·420	1·43	0·110	0·536	580	
6	7·15	5·64	—	—	0·233	0·159	0·687	0·689	0·022	0·036	0·248	0·252	419	294	12·79	—	0·392	1·38	0·058	0·500	713	
7	7·18	6·43	—	—	0·197	0·150	0·704	0·638	0·036	0·051	0·255	0·303	573	648	13·61	—	0·347	1·34	0·087	0·558	1221	
8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10·85	—	0·306	1·13	0·062	0·485	1191	
10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	13·38	—	0·404	1·42	0·081	0·690	1121	
11	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·20	—	0·384	1·24	0·063	0·640	1138	
12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·33	—	0·306	1·35	0·069	0·630	1121	
13	9·91	4·99	—	—	0·291	0·146	0·790	0·695	8·34	0·119	0·360	0·287	790	268	14·90	—	0·445	1·48	8·46	0·647	1058	Creatine 18 grm.
14	4·40	7·04	—	—	0·123	0·212	0·518	0·813	0·028	0·117	0·206	0·380	324	369	11·44	—	0·335	1·33	0·145	0·586	693	
15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·44	—	0·349	1·29	0·095	0·509	1083	
16	—	—	—	—	—	—	—	—	—	—	—	—	—	—	12·65	—	0·371	1·30	0·074	0·596	1022	
17	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10·39	—	0·306	1·22	0·46	0·473	992	

D. = 9 a.m.–9 p.m. N. = 9 p.m.–9 a.m. The amounts are expressed in grammes, the volume of urine in c.c. Creatine administered at 9 a.m.

output of creatinine was increased; in the 24 hours after the last dose it was 50 per cent. above the normal for this subject. For comparison, therefore, these observations may be summed up thus: when such large amounts of creatine are given by the mouth, the amount recovered either as creatine itself or as creatinine in the urine forms in normal man (Rose and Dimmitt, 10) 66 per cent., in rigid men 30–37 per cent., in a rigid woman 55 per cent., of the amount administered.

It is apparent that the amount of creatine given by mouth which appears in the urine of rigid subjects is not more than that observed in normal individuals; on the contrary, it is less. This result does not support the hypothesis that creatine appears in the urine in this type of rigidity because the amount of creatine in the muscles is increased. If such an increase occurs, it seems unlikely that the rigid muscles could then take up more creatine than the normal ones. On the other hand, the figures suggest that the body possesses an increased capacity for creatine. This may be associated with an actual decrease in the creatine contained in the muscles resulting from the persistent creatinuria in these cases. So far as we are aware, no figures for the creatine content of muscles in rigid subjects have been published.

It is common to regard creatine that is given by mouth and not recovered in the urine, either unchanged or as creatinine, as having been stored in the body, and since the muscles are reckoned to contain 98 per cent. of all that is in the body, it is assumed that it is stored in the muscles. But the proof that it has been absorbed and not escaped from the bowel is not furnished. The other possibility, that the missing creatine has been oxidized and its nitrogen excreted in other combinations, seems to be excluded, in some cases at any rate, by the fact that the amount of nitrogen in the urine is not correspondingly increased.

In one of Rose and Dimmitt's (10) experiments (No. 1), after creatine was added to the constant diet more nitrogen was excreted, naturally, than before, and this amounted to 14·6 grm. Of this, the creatine and additional creatinine in the urine accounted for 10·4 grm., so that possibly some of the creatine that did not appear in the urine as such or as extra creatinine was broken up in the body and accounts for the remaining 4·2 grm. of nitrogen which is otherwise unaccounted for. If that applies to the whole four grammes, it leaves no more than 2·75 grm. out of the 48 grm. of creatine taken by mouth, which, if it was absorbed, may have been retained. Similarly in their second experiment, the extra nitrogen excreted after taking creatine amounts to 10·4 grm., of which 7·5 grm. is accounted for by the creatine and additional creatinine excreted, leaving 2·9 grm. that may represent broken-up creatine, and if that is so the amount of creatine, which if it was absorbed may have been retained, is again by coincidence 2·75 grm.

Such considerations make it necessary, therefore, in studying the fate of creatine taken by mouth, to examine the urine for other constituents containing nitrogen. In our experiments so far described this was not done; in the experiments that remain to be described it was.

Experiment VI. The subject of Experiments II and IV, three months after

TABLE VII.

Case IV. Experiment VII. Total in 24 Hours.

Date.	Total Nitrogen.		Urea.		Uric Acid.		Creatinine.		Creatine.		Nitrogen as Ammonia.		Urine.		Total Nitrogen.	Urea.	Uric Acid.	Creatinine.	Creatine.	Nitrogen as Ammonia.	Urine.	
Nov.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.								
8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	8·92	15·83	0·326	1·25	0·143	0·428	779	
9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9·60	17·70	0·339	1·17	0·042	0·370	775	
10	11·74	4·99	14·50	8·89	0·277	0·140	0·845	0·738	12·16	0·194	0·214	0·295	1405	281	16·73	23·39	0·417	1·683	12·35	0·509	1686	Creatine 18 grm.
11	11·27	5·12	13·08	8·19	0·286	0·110	0·860	0·726	10·67	0·617	0·315	0·316	568	234	16·39	21·27	0·396	1·590	11·29	0·631	802	Creatine 18 grm.
12	11·31	5·61	12·67	9·73	0·253	0·138	0·872	0·766	10·66	0·950	0·298	0·302	785	278	16·92	22·40	0·391	1·640	11·61	0·600	1063	Creatine 18 grm.
13	6·48	5·50	11·40	9·52	0·220	0·158	0·741	0·735	0·193	0·059	0·294	0·345	419	312	11·98	20·92	0·378	1·480	0·252	0·639	731	
14	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·52	20·35	0·406	1·62	0·048	0·508	797	
15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10·58	19·00	0·300	1·37	0·118	0·528	1098	
16	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·28	20·60	0·353	1·42	0·055	0·526	954	
17	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1·21	0·074	—	811	
18	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1·35	0·079	—	700	

TABLE VIII.

Case V. Experiment VIII. Total in 24 Hours.

Date.	Total Nitrogen.		Urea.		Uric Acid.		Creatinine.		Creatine.		Nitrogen as Ammonia.		Urine.		Total Nitrogen.	Urea.	Uric Acid.	Creatinine.	Creatine.	Nitrogen as Ammonia.	Urine.	
Oct.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.								
25	7·53	5·58	13·61	10·15	0·321	0·209	0·726	0·594	0·052	0·038	0·273	0·254	524	365	13·11	23·76	0·531	1·32	0·090	0·527	889	
26	7·17	6·70	12·99	12·71	0·242	0·217	0·694	0·660	0·038	0·032	0·287	0·299	539	495	13·87	25·70	0·459	1·35	0·070	0·586	1034	
27	6·13	6·67	11·17	12·05	0·184	0·232	0·577	0·718	0·065	0·073	0·286	0·310	472	406	12·80	23·22	0·416	1·29	0·138	0·596	878	
29	—	—	—	—	—	—	—	—	—	—	—	—	—	—	12·39	22·75	0·380	1·21	0·069	0·451	789	
31	8·04	5·19	14·70	10·16	0·242	0·181	0·736	0·547	0·054	0·053	0·301	0·190	618	303	13·23	24·86	0·423	1·28	0·107	0·491	921	
Nov. 1	10·34	4·67	14·97	8·18	0·310	0·154	0·811	0·554	6·35	0·156	0·325	0·254	978	232	15·01	23·15	0·464	1·37	6·51	0·579	1210	Creatine 18 grm.
2	11·04	5·68	15·40	9·11	0·318	0·158	0·635	0·616	9·34	0·779	0·412	0·241	586	264	16·72	24·51	0·476	1·25	10·12	0·653	850	Creatine 18 grm.
3	11·66	6·28	14·42	9·67	0·301	0·190	0·881	0·712	8·66	1·53	0·424	0·324	736	294	17·94	24·35	0·491	1·59	10·19	0·748	1030	Creatine 18 grm.
4	7·92	3·91	13·49	7·14	0·258	0·097	0·985	0·490	0·451	0·072	0·419	0·190	394	154	11·83	20·63	0·355	1·47	0·523	0·609	548	
5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·33	20·4	0·404	1·52	0·140	0·329	788	
6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·04	19·14	0·439	1·52	0·108	0·489	870	
7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11·16	20·1	0·405	1·36	0·152	0·394	1049	

D = 9 a.m.–9 p.m. N = 9 p.m.–9 a.m. The amounts are expressed in grammes, the volume of urine in c.c. Creatine administered at 9 a.m.

the latter experiment, was put on a diet again for a fortnight, during which the urine, collected for two twelve-hour periods ending at 9 a.m. and 9 p.m. daily, was analysed as shown in Table VI. A single dose of 18 grm. of creatine was then given, and nine days later this was repeated.

After the first dose the additional creatine and creatinine excreted corresponds to 8·3 grm. of creatine, and this would account for 2·6 out of the 5·4 grm. of additional nitrogen excreted; if the 2·8 grm. of the nitrogen remaining to be accounted for represents creatine broken up in the body, that would account for another 8·7 grm. of creatine, making 17 grm. in all. Only about 1 grm. of creatine, therefore, may be said to have been retained if absorbed.

After the second dose, the additional creatine excreted, 8·5 grm., contains 2·7 grm. out of the 3·6 grm. of nitrogen excreted above the dietary rate and leaves just less than one gramme unaccounted for; if this were due to the breakdown of absorbed creatine, it would represent about 2·8 grm. of absorbed creatine, leaving about 6·5 grm., which if absorbed must have been retained.

Experiment VII. The same subject was given a similar dose of creatine on three successive days, to see whether any change in the amount retained could be effected in this way.

When the figures (Table VII) for the total nitrogen and creatine are reckoned as in Experiment VI, it can be seen that the additional nitrogen excreted leaves a margin of some 10 grm. more than that accounted for by the additional creatine and creatinine in the urine, and that these latter account for all the creatine ingested except about 10 grm. So that the nitrogen in the urine is increased much more than is necessary to account for the creatine which was not excreted unchanged or as extra creatinine; and it is unjustifiable to assume that any was retained or stored in the muscles.

In a similar experiment to this last, done on the subject of Experiments I and III (Table VIII, Case V), the amount of creatine excreted on the second and third days is definitely greater than on the first. He had had no creatine for three months, and the amount excreted on the first day, 6·5 grm., is similar to the amount excreted three months earlier after 18 grm. had been given. Reckoned as before, the additional creatine and creatinine in the urine account for 27·8 grm. and the nitrogen in this accounts for all the increase in the total nitrogen of the urine that results from the taking of creatine. Of the nitrogen of the missing 20 grm. of creatine there is no trace. If the creatine was absorbed it must have been stored in the body.

In order to have some results under similar conditions and with similar doses from normal subjects, two students thoroughly competent to appreciate the nature of the experiment volunteered to collaborate as subjects.

One of these (Experiment IX, Table IX) received a dose of 18 grm. of creatine on three successive days when he had been on a diet free from creatine, creatinine, and purine derivatives for a week. He excreted in five days creatine and additional creatinine accounting for 36·2 grm. of creatine, which would add 11·2 grm. of nitrogen more than on the diet before the dose; that is, 6·5 grm. in

TABLE IX.

Subject C. Experiment IX.

Date	Total Nitrogen.		Urea.		Uric Acid.		Creatinine.		Creatine.		Nitrogen as Ammonia.		Urine.		Total Nitrogen.	Urea.	Uric Acid.	Crea-tinine.	Creatine.	Nitrogen as Ammonia.	Urine.	
1926	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.								
17	7·6	5·3	13·6	10·56	0·239	0·124	0·881	0·779	—	—	0·338	0·282	760	376	12·9	24·2	0·363	1·66	—	0·620	1136	
18	6·18	6·12	10·82	11·00	0·232	0·175	0·890	0·794	—	—	0·315	0·309	448	342	12·3	21·8	0·407	1·68	—	0·624	790	
19	12·4	5·98	15·40	10·60	0·372	0·163	0·984	0·823	10·28	0·290	0·383	0·301	958	282	18·38	25·9	0·534	1·81	10·57	0·684	1240	Creatine 18 grm.
20	13·2	5·86	16·1	9·6	0·335	0·154	0·953	0·877	10·56	0·813	0·428	0·360	1009	306	19·06	25·7	0·488	1·83	11·37	0·788	1315	Creatine 18 grm.
21	12·6	5·50	16·0	8·5	0·350	0·139	1·030	0·872	11·36	1·232	0·404	0·341	855	210	18·14	24·5	0·489	1·90	12·59	0·745	1065	Creatine 18 grm.
22	7·3	7·50	12·7	13·6	0·241	0·120	0·870	0·787	0·508	0·209	0·351	0·331	338	443	14·82	26·3	0·361	1·66	0·72	0·682	781	
23	7·6	5·06	13·65	12·9	0·280	0·158	0·853	0·937	0·106	0·150	0·493	0·357	386	730	14·66	26·4	0·438	1·79	0·26	0·850	1116	
24	7·1	5·88	12·60	10·92	0·243	0·148	0·810	0·860	—	—	0·405	0·358	634	323	12·98	23·5	0·391	1·67	—	0·763	957	
25	6·67	7·00	11·53	13·11	0·262	0·193	0·886	0·835	—	—	0·346	0·315	515	748	13·67	24·6	0·455	1·72	—	0·661	1263	

TABLE X.

Subject E. Experiment X.

Date.	Total Nitrogen.		Urea.		Uric Acid.		Creatinine.		Creatine.		Nitrogen as Ammonia.		Urine.		Total Nitrogen.	Urea.	Uric Acid.	Crea-tinine.	Creatine.	Nitrogen as Ammonia.	Urine.	
Dec.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.	D.	N.								
2	7·86	7·83	14·86	14·48	0·268	0·256	0·804	0·777	—	—	0·395	0·385	605	548	15·69	29·34	0·524	1·581	—	0·780	1153	
3	7·53	7·95	14·10	14·34	0·285	0·238	0·797	0·743	—	—	0·371	0·453	638	487	15·48	28·44	0·523	1·540	—	0·824	1125	
4	7·61	8·68	13·48	15·80	0·274	0·211	0·807	0·823	—	—	0·356	0·465	646	488	16·29	29·28	0·485	1·630	—	0·821	1134	
5	8·50	7·80	15·68	14·22	0·276	0·204	0·796	0·746	—	—	0·415	0·432	414	381	16·30	29·90	0·480	1·542	—	0·847	795	
6	12·32	7·21	17·10	13·22	0·396	0·152	0·914	0·767	8·08	0·078	0·415	0·398	921	346	19·53	30·32	0·548	1·681	8·160	0·813	1267	Creatine 18 grm.
7	10·45	9·56	12·25	16·67	0·294	0·217	0·785	1·078	9·00	0·639	0·376	0·529	939	569	20·01	28·92	0·511	1·863	9·639	0·905	1508	Creatine 18 grm.
8	11·85	8·08	14·05	13·74	0·305	0·174	0·943	0·961	10·48	1·026	0·517	0·472	902	471	19·93	27·79	0·479	1·904	11·506	0·989	1373	Creatine 18 grm.
9	7·21	7·95	12·58	14·12	0·241	0·212	0·940	0·891	0·116	0·095	0·437	0·452	380	371	15·16	26·70	0·453	1·831	0·211	0·889	751	
10	8·17	7·26	15·31	13·28	0·353	0·211	0·833	0·820	0·061	0·093	0·304	0·384	533	370	15·43	28·59	0·564	1·653	0·153	0·688	903	
11	6·26	8·40	11·78	15·61	0·266	0·227	0·800	1·060	0·067	0·086	0·342	0·469	686	524	14·66	27·39	0·493	1·860	0·153	0·812	1210	
12	9·04	8·00	16·70	14·79	0·321	0·175	0·918	0·832	0·025	0·065	0·543	0·487	603	628	17·05	31·49	0·496	1·750	0·090	1·030	1231	
13	8·70	7·01	14·85	12·40	0·279	0·171	0·839	0·820	0·082	0·049	0·495	0·448	1137	377	15·71	27·25	0·450	1·650	0·131	0·943	1514	
14	7·87	7·62	13·59	13·53	0·348	0·252	0·905	0·795	—	—	0·432	0·415	583	424	15·49	27·12	0·590	1·700	—	0·847	1007	
15	8·77	7·00	15·55	12·60	0·325	0·162	0·940	0·793	—	—	0·494	0·361	1105	420	15·77	28·15	0·487	1·783	—	0·855	1525	

D = 9 a.m.–9 p.m.   N = 9 p.m.–9 a.m.   The amounts are expressed in grammes, the volume of urine in c.c.   Creatine administered at 9 a.m.

other combinations. (The figures of the table work out to be 22·7, but the nitrogen intake in the daily diet was increased by one gramme on the third day, i. e. the 19th.) The creatine which did not appear in the urine would not contain as much as this. No evidence for any storage of creatine is given by this subject any more than by Case IV. Here, again, the amount of creatine excreted after the second and third doses is greater than after the first.

The other subject, E. (Table X), who went through precisely the same preparation and routine and received the same amount of creatine similarly distributed, excreted as creatine and additional creatinine 9·8 grm. of nitrogen. The actual increase in the nitrogen output, as compared with the days before the treatment, was 10·8 grm., so that only 1 grm. of additional nitrogen is left to account for the 20 odd grammes of creatine that did not appear in the urine as creatine or additional creatinine. Clearly, therefore, a large amount of creatine was either retained in the body or was not absorbed.

According to these results, it appears that in both normal and rigid subjects two types of response to the administration of creatine in large doses may occur. In one type creatine, if absorbed, is retained in the body; in the other, strictly speaking, it is not retained. In the latter the increased nitrogen output suggests that it was all absorbed and that that which was not excreted as creatine or creatinine was broken down completely.

Additional points of interest with regard to the amount of creatine excreted unchanged after large doses are shown by the figures in these experiments. On the first occasion, when 18 grm. of creatine were administered to the rigid subjects, Cases IV and V (Table IV), the amounts appearing unchanged in the urine were 6·34 and 5·84 grm. respectively. In the last experiment carried out on these two subjects, when similar doses were given on three successive days, after the first of these doses the creatine in the urine was 12·35 and 6·5 grm. respectively. In both instances an interval of about three months had elapsed between the experiments. In the latter case no creatine had been given to this subject during this period, but in the former, where such a striking difference was observed, during the six weeks prior to this last experiment 18 grm. of creatine had been administered on eight occasions. Figures for the creatine excreted as such after these doses are given below:

Oct. 4	7·74 grm. creatine	
Oct. 13	8·46 „ „	
Oct. 21		some urine lost.
Oct. 22	9·78 „ „	
Oct. 23		some urine lost.
Nov. 10	12·35 „ „	
Nov. 11	11·29 „ „	
Nov. 12	11·61 „ „	

In the other rigid case and in the two normal subjects, after the administration of creatine in 18-grm. doses on three successive days, the amount excreted during the 24 hours following each dose increased so that more was excreted

after the second dose than after the first. This increase was most marked in the rigid case: 6·5 grm. were excreted after the first dose, 10·12 grm. after the second. Following the third dose the amount excreted was practically the same as after the second. In the normal subjects, however, a further increase was observed after the third dose of creatine.

It does not seem likely that these responses to creatine are due to rates of elimination or to the diuresis which follows creatine. After the creatine was taken, much the greater portion, which appeared unchanged in the urine, was eliminated during the first twelve hours. With successive doses the proportion excreted during the second twelve hours increased to a small degree; in the most marked instance the amount excreted in the second period was 1·2 grm., whereas 11·3 grm. were excreted during the first (Table IX). The kidneys therefore, were not overworked during the second twelve-hour period. Creatine is a diuretic, but the relation between the output of water and the amount of creatine in the urine is not constant, e. g. in the normal subject C (Table IX) less creatine was excreted after the second dose, when the volume of urine was greater, than after the third dose, when the output of urine was not so great. It seems possible, therefore, that these results are in some way associated with the capacity of the body to deal with creatine. It cannot, however, be simply a matter of storage in the muscles, since the same results were obtained whether there was evidence of creatine retention or not.

The output of creatinine was also increased after creatine. This increase usually appeared after the first dose except in Case V (Table IX), when it did not appear until after the third dose. In every instance the increase persisted for several days. These results undoubtedly confirm the observations of Rose and Dimmitt, which are interpreted by them as proof of the transformation of creatine into creatinine within the body, and such an interpretation has been accepted by Hunter (11). It must be pointed out, however, that in the figures presented in this paper there is also evidence that an increase in the output of urea, uric acid, and ammonia accompanies the increase in the creatinine.

Summary.

1. In subjects manifesting marked degrees of Parkinsonian rigidity creatinuria occurs regularly. The amount excreted by the cases examined, expressed as a fraction of the body-weight, appears to be related to the degree of rigidity. The rate of excretion is lowest during the night, when the muscular system is inactive. In these respects it resembles the output of uric acid, both in these cases and in the normal subject.

2. After single doses of creatine (18 grm.) rigid cases excrete less of the ingested creatine than do normal subjects. When three such doses of creatine were taken on three successive days by one rigid case and two normal subjects, the output of creatine was greater after the second and third doses than after the first. This difference in the amount excreted after the first and second doses

was most marked in the rigid case. In another rigid case, similarly treated, no such increase after successive doses was observed, but large amounts of creatine had been given to this subject during the previous six weeks. Even when creatine was taken by mouth in these large doses, part of it always failed to appear unchanged in the urine both in normal and rigid subjects.

3. In one rigid case and in one normal subject, after 18-grm. doses of creatine taken on three successive days, the increase in the total nitrogen output in the urine accounts for all, or almost all, the extra nitrogen taken in the form of creatine. This suggests that the creatine was all, or almost all, absorbed and that which was not absorbed was broken down completely.

In another rigid case and a normal subject, a considerable part (20 grm.) of the 54 grm. of creatine taken in doses of 18 grm. on three successive days cannot be accounted for in the urine at all. If it was absorbed it must have been retained.

These differences do not appear to be associated in any way with the abnormal state of the muscular system.

4. Creatine in large doses increases the output of creatinine both in rigid cases and in normal subjects; the greatest increase was observed in a rigid female. In some instances an increase was also observed in the output of urea and uric acid.

The precise significance of these results is not at present apparent, but the interest to be attached to them is greatly enhanced by the recent work of Fiske and Subbarow and P. and G. P. Eggleton, demonstrating the presence of a labile compound of phosphoric acid and creatine in muscle, which is broken down during activity and built up again during rest.

It is a pleasure to acknowledge our indebtedness to Professor Arthur Hall for the provision of cases, to Professor Leathes for his interest and advice throughout the investigation, and to Mr. W. F. Carlisle and Mr. F. Ellis, who acted as subjects for two of the experiments.

We should like also to express our thanks to the Medical Research Council, which defrayed the expenses of this research.

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'CONGENITAL' ANEURYSM OF THE CEREBRAL ARTERIES[1]

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With Plates 13 and 14

THE occurrence of aneurysms of the circle of Willis and its branches has already formed the subject of a considerable literature. In this country alone a very large number of such cases has been reported during the last thirty years. Turnbull (1, 2) and Fearnsides (3) have contributed largely to our knowledge of the pathological aspect of the lesions, while Symonds (4) has shed a great deal of light upon their clinical significance, stressing the fact that they can often be diagnosed in the recoverable 'leak' stage which so frequently precedes the fatal rupture. As regards pathogenesis, Fearnsides classifies these aneurysms under four headings, viz.:

(*a*) Those due to infective embolism (mycotic aneurysms in malignant endocarditis).

(*b*) Those associated with, and probably due to, gross atheromatous changes in the cerebral vessels.

(*c*) Those due to syphilis.

(*d*) Those occurring in patients who have no obvious source of embolism, exhibit no evidence of syphilis, and whose cerebral arteries, apart from the aneurysm, are relatively or completely normal. These, a large group, form the so-called 'congenital' aneurysms.

At St. Bartholomew's Hospital during the last five years (1922–7) nineteen cases of basal cerebral aneurysm have come to post-mortem, in seventeen of which rupture of the aneurysm has been the cause of death. In five of these cases the aneurysm has been due to infective embolism in malignant endocarditis; two of the patients showed gross cerebral arteriosclerosis, and their aneurysms were probably 'atheromatous' in origin; the remaining twelve appeared to belong to the 'congenital' group. In none of them was there clinical or pathological evidence of syphilis. Syphilis as a basis of cerebral aneurysm is stated by Turnbull to be rare.

In each of three cases (one belonging to the 'endocarditic' and two to the 'congenital' group) two aneurysms were present, one of which had ruptured.

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In another of the latter group (Case No. III in the present report) three saccular aneurysms in varying stages of development were present in the branches of the circle of Willis. The largest of them had ruptured and caused death.

It is of interest to note the age at which the fatal rupture occurred in these various types of case. The average age at death of the 'endocarditic' group was 25 (actual ages: 36, 26, 26, 25, 13); of the 'arteriosclerotic' group it was 58 (actual ages: 60 and 56); while of the 'congenital' group it was 43, the individual ages being 63, 57, 52, 49, 48, 46, 43, 42, 30, 25, 21. The average age at death in cases of intracerebral (lenticulo-striate and pontine) haemorrhage over this period of five years was 58.

These figures indicate that rupture of basal aneurysm, though most common in middle life, tends to occur considerably earlier than ordinary lenticulo-striate and pontine haemorrhage. A review of the literature supports the statement that cerebral haemorrhage in a patient aged less than 50, who is not markedly arteriosclerotic, is probably attributable to rupture of a basal aneurysm, the latter either due to malignant endocarditis or belonging to the 'congenital' group. There are, of course, other possible causes, such as trauma and certain blood diseases, but, compared with basal aneurysms, these other causes are extremely rare.

I have thought that the following three cases are worth reporting in some detail, because in each of them the aneurysms appeared to be of the same pathological type (in Cases Nos. I and II they had precisely the same anatomical site), and because in Case No. III, in addition to the multiplicity of cerebral aneurysms, there were present in the body congenital arterial abnormalities in the form of coarctation of the aorta, bicuspid aortic orifice, and fenestration of the mitral cusps. Cerebral haemorrhage has been a common cause of death in the cases of coarctation of the aorta hitherto reported, and Parkes Weber (5), Woltman and Shelden (6), and Parker (7) have reported cases in which the haemorrhage was attributable to rupture of aneurysms of this type. The coexistence with them of arterial maldevelopments might be adduced to strengthen the hypothesis of Eppinger (8) that aneurysms of the cerebral arteries may have a congenital basis in maldevelopment of the contractile tissue at certain points in the vessel-wall. These three patients were under the care of Dr. H. Morley Fletcher and Sir Percival Horton-Smith Hartley, to whom I am indebted for permission to make use of their clinical notes.

Case Reports.

Case I. D. P., female, 30, single; occupation: parlourmaid. She was admitted to St. Bartholomew's Hospital on January 22, 1927, in a stuporous condition.

The history, elicited from a relative, was as follows:

She had been in her usual health till January 7. On January 8, while up and about, she complained of sudden violent pain in the head, commencing in

the occipital region and spreading over the vertex. She vomited at the onset and after every meal for four days. The pain lasted until January 15, during which time she remained in bed. On January 16 she felt better, and by January 20 she was 'herself again' and went for a walk. On January 22, at 8.30 a.m., she complained that she had had a restless night, though no definite cause for this could be elicited. At 10.45 a.m. she was found in bed in a semi-conscious condition. She could recognize her friends and was able to speak with difficulty. She vomited twice that day before removal to hospital.

Family and Past Histories. She was one of fifteen children. Had always been healthy. There was no history of old or recent injury to the head.

Condition on Examination. She was a well-nourished young woman, pale, and in a semi-conscious state, from which she could be roused with difficulty to answer questions. Speech was slow and indistinct. There was conjugate deviation of the eyes to the right. The pupils, optic disks, and retinae were normal. To rough testing, there was hemianopia of the left fields. There was weakness of the whole left face and paresis of the left upper and lower limbs. The tendon reflexes on the left side were feeble, with the exception of the ankle-jerk, which was brisk. There was no clonus. The left plantar response was extensor, and the abdominal reflexes were absent. On the right side, motor power and reflexes were normal. Sensation appeared to be unimpaired on either side. There was no head-retraction nor neck-stiffness, and Kernig's sign was absent at this time. The heart and lungs were normal. The blood-pressure on admission was 170/95; two days later the systolic pressure had fallen to 145, the diastolic remaining the same as before. She was obstinately constipated and incontinent of urine, which was of good colour and specific gravity; it contained a trace of albumin and sugar, but no casts. She had slight irregular fever, ranging from 99° to 101 °F. A lumbar puncture was performed on the day of admission. The fluid obtained was evenly bloodstained and under pressure. After centrifugalizing, the supernatant fluid was clear and practically colourless. The Wassermann and Sigma tests (C.S.F.) were negative.

On January 25 some head-retraction and a definite Kernig's sign were present. The patient complained of pain in the occipital region. Mentally she was clear and talked rationally to her friends. There was now some blunting of cutaneous pain sensation on the left side, but no actual loss. Conjugate deviation to the right persisted. The pupils were contracted and sluggish in reaction. Lumbar puncture was repeated; again a haemorrhagic fluid was obtained, and the supernatant fluid was definitely yellow.

On January 28 there was definite impairment of sensation to pin-prick down the whole of the left face, trunk, arm, and leg. Other sensations could not accurately be tested, as it was difficult to hold the patient's attention. She complained constantly of pain in the occipital region and back.

On February 3 she became restless and 'rambled' at times. She still complained frequently of occipital pain. Movement in the left hand was improved. She was completely incontinent of urine and faeces. Lumbar puncture once more produced a deeply blood-stained fluid under pressure.

From now on till February 24 her condition remained stationary in spite of repeated lumbar puncture. The diagnosis rested between aneurysm and a tumour into which haemorrhage had occurred. In view of the latter possibility, and because the site of the lesion could be localized to the lower part of the right hemisphere, Mr. Rawling performed an exploratory operation on February 24. A large flap was turned down in the right temporal region, and a trephine hole was made posterior to the middle meningeal artery. On chipping away the bone, tense bluish dura was exposed, and the brain bulged into the opening. Owing to the general condition of the patient the operation had to be terminated rapidly from this point. After operation she did not completely regain consciousness, and died early in the morning of February 25.

Post mortem. A post-mortem examination, of the head only, was made the same day. There was extensive subarachnoid haemorrhage, most marked over the convexity of the right hemisphere. Blood was also present in the interpeduncular space, and around the brain-stem and postero-inferior aspect of the cerebellum.

The brain was removed for section after hardening in formalin. On incising transversely the right cerebral hemisphere, an extensive excavation filled with blood-clot was found occupying the area shown in the diagram (Fig. 2). It was obvious that the blood had passed upwards and backwards from the Sylvian fissure. It had ploughed up the inner aspect of the temporo-sphenoidal lobe and part of the insular cortex, claustrum, and lenticular nucleus, damaging also the posterior limb of the internal capsule. It extended posteriorly into the white matter lying between the external capsule and the thalamus, and upwards into the deeper layers of the parietal cortex. It had penetrated into the lateral ventricle, which contained fluid blood.

FIG. 2. *Case I.* Sketch to show area of brain ploughed up by haemorrhage.

On clearing away a mass of blood-clot from the right Sylvian fissure, a saccular aneurysm measuring about 2 cm. in length by 1 cm. in diameter was found lying in the fork between two cortical branches of the middle cerebral artery. Its position and appearance are shown in the photograph (Pl. 13, Fig. 1). A rupture about 3 mm. in diameter had occurred at its distal extremity. The site of the rupture was surrounded, and the sac itself partially filled, by blood-clot. The wall of the aneurysm showed patchy atheromatous changes, but the rest of the cerebral vasculature was macroscopically normal. The aneurysm with its parent trunk, the left middle cerebral artery, and portions of the brain substance were preserved for microscopic examination.

Histological. The sac contained laminated blood-clot. Its wall was thin and consisted mainly of fibrous tissue and connective tissue cells, though the 'internal elastic lamina' of the parent trunk was continued for a short distance into the sac, ending there as a few thin irregular strands. There was no trace of muscle tissue in the wall of the aneurysm. The sac showed differentiation into two layers corresponding apparently to the tunicae 'intima' and 'adventitia'; in its proximal portions, the boundary between the two layers was marked by the remains of the elastic tissue. The 'intima' was greatly thickened, particularly in those places where the adventitia was most attenuated; it was composed of connective tissue cells, spindle-shaped, oval, or branched, and of a certain amount of formed fibrous tissue. At one point of the circumference it

was markedly degenerated, fatty material being present in quantity. No calcification was visible. The adventitia consisted of a layer of fibrous tissue, in places extremely thin; there was no evidence in it of inflammatory infiltration, and the small vessels penetrating its outer aspect, though surrounded by organizing blood-clot, displayed no abnormality. At the origin of the aneurysm from its parent trunk, the most striking feature was the almost sudden disappearance of the muscle-tissue. The parent vessel itself and the other vessels examined, including the smallest arteries of the intimate cerebral vasculature, showed no evidence of syphilitic nor of arteriosclerotic changes.

It would seem that in this case leakage of the aneurysm had occurred, probably in an intermittent manner, over a period of six weeks, until a considerable area of the brain substance was destroyed. The temporary improvement in the patient's symptoms between January 16 and 22 forms a striking feature of the clinical history and corresponds with the remissions noted in each of Symonds's cases.

In the following case (Case No. II) the picture was different, the first rupture being sufficiently severe to cause death within two days.

Case II. A. J., female, 49, married. Admitted to St. Bartholomew's Hospital on May 20, 1927, in a comatose condition.

History (elicited from her husband). She had been well except for occasional complaints of giddiness until the day of admission. That afternoon she was found on the floor unconscious. She had vomited into a sink (presumably before losing consciousness) and on to the floor afterwards.

Past history. She had had exophthalmic goitre, treated successfully by operation. She had been married 23 years. There were no children, and there was no history of miscarriages.

Condition on examination. The patient was a thin, sallow woman; comatose. She could be roused very slightly by stimulation, but did not speak. She was afebrile at this time. There was no head-retraction. The eyes were deviated to the right; the pupils were equal, not contracted, and reacted normally. The left arm and leg were immobile and slightly spastic. The arm reflexes were absent on the left, present normally on the right. The left abdominal reflexes were absent, the right being present. Both knee-jerks and the right ankle-jerk were brisk; the left ankle-jerk was feeble. The right plantar response was flexor, the left extensor. The heart was not obviously hypertrophied. The blood-pressure was 150/85. The urine contained a trace of acetone, but no protein or sugar. A lumbar puncture was performed and 20 c.c. of evenly blood-stained fluid were withdrawn under slightly increased pressure.

On May 21, the patient was deeply comatose with stertorous respiration. The axillary temperature rose to 105° F. on the left side, 106° F. on the right. The physical signs remained the same, except that the left knee-jerk could no longer be elicited. The urine contained a trace of albumin and sugar. The patient died that evening.

Post mortem. A post-mortem examination was performed on the following day. The heart weighed 9½ oz.; the left ventricle showed a little 'concentric' hypertrophy; the valves and coronary arteries were normal. The aorta showed a little patchy atheroma in its descending arch. The kidneys were of normal size; their capsules stripped with slight difficulty, leaving a very finely granular surface, but the cortex was not diminished, and the vessels did not appear unduly prominent. Microscopic examination revealed a few atrophied glomeruli, but no arterioles showing typical arteriosclerotic changes were seen. The lungs showed bilateral basal broncho-pneumonia.

The brain. On the right side the convolutions were flattened; there had been extensive subarachnoid haemorrhage over the right hemisphere and over the anterior portion of the left hemisphere. The right Sylvian fissure was distended with clot, and this was also present in quantity round the structures of the interpeduncular space, over the ventral surface of the pons, and, to a lesser extent, over the cerebellum. On the right middle cerebral artery in the Sylvian fissure was a ruptured aneurysm; it lay in precisely the same anatomical position as that described and photographed in Case No. I. It also had ruptured at its distal extremity. It measured about 1 cm. in length by 0·5 cm. in diameter. In its walls were a number of small plaques of atheroma, but the rest of the cerebral arteries to naked-eye examination did not appear abnormal. The haemorrhage arising from the rupture had passed into the Sylvian and Rolandic fissures, which it had distended to a remarkable extent, but although the haemorrhage had been a copious one, the brain substance itself was only relatively slightly damaged. A horizontal section of the brain taken at the level of the globus pallidus showed that the insular cortex and its internal relations (the basal ganglia and its capsules) were condensed together as a result of the distension of the Sylvian fissure, but were not actually ploughed up by the haemorrhage (see Fig. 3). The inner portion of the temporo-sphenoidal lobe and a portion of the corona radiata were macerated, and this, together with the compression of the internal capsule, presumably accounted for the complete left hemiplegia. The haemorrhage had not penetrated into the ventricle.

FIG. 3. *Case II.* Sketch to show distension of right Sylvian fissure and damage to brain by haemorrhage.

An interesting feature of this brain was the fact that each of the perforating arteries in the lenticular nucleus on the right side showed an obvious 'cuff' of blood-clot occupying and distending the Virchow-Robin space. It was as if the spaces had been injected with blood under considerable pressure, and this appearance was present even in the case of the smallest visible branches. In addition, there were at the periphery of the main extravasation a number of small 'secondary' haemorrhages of the type discussed by Hassin (9). On the left side the brain substance and vessels appeared macroscopically normal.

Histological. The wall of the sac was cut transversely. It consisted of moderately dense fibrous tissue in which an occasional thin elastic fibril could be

seen. Muscular elements appeared to be entirely absent. The wall of the sac showed differentiation into two distinct layers. The inner coat, apparently continuous with the intima of the parent trunk, was less dense and more cellular than the outer, and was thickest in those portions of the circumference where the latter was most attenuated; in its deepest part degenerative (fatty) changes could be seen. Its cellular constituents consisted of fibroblasts and connective tissue cells, many of them stellate in form; it contained also a certain amount of formed fibrous tissue. No calcification was demonstrable. There was no evidence of active inflammatory changes in the wall of the sac, and the parent trunk and the branches on either side of the sac appeared quite normal. Investigation of other branches of the circle of Willis and of the smallest intracerebral vessels revealed no evidence of syphilis nor marked arteriosclerosis.

Case III. F. B., male, 21. Clerk. Admitted to St. Bartholomew's Hospital on October 28, 1926. He was brought to hospital by the police, having had a 'fit'.

History. He arrived at his office at 9 a.m., apparently in normal health, though his friends noticed that he seemed 'excited'. At about 9.15 a.m. he complained of pains in the head, chiefly on the right side, and of dizziness. He collapsed and became unconscious, and 'began to throw his arms about'. Did not foam at mouth, bite his tongue, nor pass urine. He was removed to hospital, and on arrival (10 a.m.) appeared to have quite recovered.

Previous history. When aged 2½ he was admitted to the Children's Hospital, Great Ormond Street, and later to University College Hospital because of having an 'under-developed heart'. He had remained in good health until April 1924, when he had 'a kind of stroke'—severe headache (unlocalized) with temporary loss of use of the limbs. A doctor who saw him then told him his heart was 'bad', and warned him against over-exertion. Following that attack he had several others, separated by weeks or months. Each attack was preceded by severe headache and giddiness, followed in a few minutes by collapse with loss of consciousness and jerky movements of the arms. During the six weeks preceding admission he had vomited occasionally. He had been much occupied with, and excited by, local mission meetings. According to his relatives he 'was at church night and day'. There was no history of trauma.

The 'family' history revealed no history of congenital defects and nothing to suggest syphilis.

Condition on examination (10 a.m.). A pale, thin, unhealthy looking individual. Fully conscious and able to give a rational account of himself. No twitchings. No pareses. Examination of the chest showed the following abnormalities: The heart was enlarged slightly to the left. A loud systolic murmur was present at the apex, conducted outwards and audible over the whole praecordia. The second aortic sound was markedly accentuated. No distended superficial arteries, comparable to those seen in Parkes Weber's case, were observed clinically.

Before examination was completed the patient again lost full consciousness, though at 11.25 a.m. he would obey directions, such as to open his mouth. The right arm was spastic and exhibited curious movements, the patient smacking with his right hand the right side of his head with great force and frequency. The left arm and the legs were flaccid and showed no spontaneous movements. The eyelids were firmly closed. The pupils were small, equal in size, and reacted to light. Both eyes were externally rotated. There was definite optic neuritis on the right side, and a large triangular subhyaloid haemorrhage to the outer side of the disk; the left fundus was normal except for venous engorgement. The biceps, triceps, and supinator tendon-jerks were bilaterally present and equal. The abdominal reflexes were absent; the right knee-jerk was brisk, the left very feeble. The right plantar response was flexor, the left extensor. The

'clonic' movements of the right arm continued for half an hour (till 12.15 p.m.). The patient became progressively more comatose and died at 12.25 p.m. Just before death he became deeply cyanosed and coughed up a quantity of pinkish frothy material.

Post mortem. A post-mortem examination was made on the following day. There was coarctation of the aortic isthmus, the lumen being narrowed to the thickness of an ordinary pencil for one inch of its length just distal to the origin of the left subclavian artery. The mitral cusps were fenestrated and the aortic orifice was bicuspid. The lungs showed signs of acute pulmonary oedema.

On opening the cranium, extensive subarachnoid haemorrhage was seen to extend over the vertex and round the structures at the base. The medulla and upper cervical cord were ensheathed with clot. The haemorrhage had arisen from a saccular aneurysm situated at the origin of a branch from the main trunk of the right anterior cerebral artery about 4 cm. from its commencement. In the fresh state this aneurysm was about 3 cm. in diameter. A small opening was present at its distal extremity, from which blood had escaped into the subarachnoid space and into the substance of the right frontal lobe. This area of the brain was extensively ploughed up, and the right lateral ventricle was distended with dark blood-clot. Besides the aneurysm which had ruptured, the basal arteries showed the following abnormalities: (*a*) an unruptured aneurysm about 0·5 cm. in diameter at a bifurcation of branches of the right anterior cerebral; (*b*) a minute saccular dilatation suggesting a commencing aneurysm between the basilar artery and the origin of the left posterior cerebral and superior cerebellar arteries. The position of this is shown diagrammatically in Fig. 4, which also shows (*c*) a fusiform dilatation of the terminal centimetre of the left vertebral artery. There were thus three saccular aneurysms in the basal cerebral arteries of this case, in addition to fusiform dilatation of another vessel. In view of the fact that these vessels might show various stages in the pathogenesis of aneurysm, it was thought advisable to cut serial sections of each as well as of intervening normal arteries. It should be noted that the fusiform dilatation referred to was the only part of the cerebral vasculature which showed macroscopic atheromatous changes. The trunk of the basilar throughout its length showed the 'semitranslucency' of a normal cerebral artery.

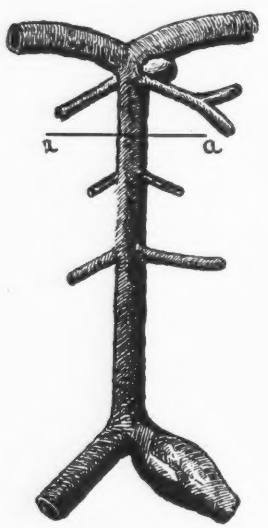

FIG. 4. *Case III.* Diagram of basilar artery to show position of the minute saccular aneurysm between the origins of the left posterior cerebral and superior cerebellar arteries; also fusiform dilatation of left vertebral artery just proximal to commencement of the basilar.

Histological. The walls of the two larger aneurysms showed a similar structure to that of the sacs described under Cases Nos. I and II. Each appeared to consist only of two coats, viz. adventitia and markedly thickened intima. The muscular tissue of the parent artery seemed to end abruptly at the point of dilatation, but the internal elastic lamina could be traced for a short distance into the sac, in the proximal portion of which it formed the boundary between the two coats.

There was a considerable amount of necrosis in the deepest parts of the intima, and in places calcification had occurred. There was no evidence of a syphilitic, nor of a mycotic origin for the aneurysms.

In the case of the smallest aneurysm, that on the basilar artery, serial sections were made from the level shown in the diagram (Fig. 4, *a–a*), up to the point where the posterior cerebral arteries separated on their outward course.

Below the level of the dilatation the basilar artery and its branches showed no abnormality. On approaching the sac from below upwards, the first change noticed was a local thickening of the intima, comparable to that seen in ordinary nodular sclerosis. It was formed by a subendothelial hyperplasia of connective tissue cells, the endothelial lining of the lumen being intact. A little farther up, and near the origin of the left superior cerebellar artery, the internal elastic lamina was split into several thin layers, which, however, appeared continuous around the circumference of the dilatation.

At the actual level of origin of the above artery the middle coat of its parent trunk displayed a striking local change, the appearances presented being as follows: At a single point in the circumference of the sac the muscle-fibres appeared shrunken to about a third of their normal width, the spaces between the shrunken fibres being occupied by large numbers of connective tissue cells of various types. It seemed as if there had occurred a quite local muscular atrophy at this point. In addition, some of the fibres appeared shredded and as if torn across. Indeed, in one small zone there seemed to be a complete absence of muscle strands, the media at this point consisting entirely of connective tissue cells. This area of muscular defect was strictly localized to a point corresponding to the level of origin of the left superior cerebellar artery, and it represented on the basilar artery the point of maximum convexity of the sac shown in Fig. 4. In longitudinal extent it was present over a distance equivalent to sixty 5-μ serial sections. Above, below, and on either side of this point, the middle coat of the basilar seemed to be perfectly normal, though the intima was markedly thickened, both longitudinally and transversely, over a considerably wider area. At the level of the most marked medial change, there appeared also to be a small breach in the continuity of the internal elastic lamina. This, however, was present only in five of the serial sections, whereas the muscular lesion, as stated above, was considerably more extensive. There was no calcification, and comparatively little evidence of fatty change could be detected in this region, either in the media or the subjacent intima. Lymphocytic and plasma-cell infiltrations were absent from this as from the other arteries examined.

The relative scarcity of fatty changes, as well as the focal character of the medial lesion, suggested that this was due to a primary change in the muscle-coat rather than being a sequel to ordinary nodular sclerosis. Where the latter disease spreads outwards to involve the media, there are usually well-marked fatty deposits in the subjacent portion of the intima.

The above findings may be summarized by saying that there was in the basilar artery a focus of diseased or defective muscle-coat, together with a more localized breach in the continuity of the internal elastic lamina; these changes occurred close to the point of origin of the left superior cerebellar artery from its parent trunk. The area so affected corresponded with the point of maximum convexity of the saccular dilatation shown diagrammatically in Fig. 4.

The histological appearances in the zone of medial deficiency are shown in the photographs (Pl. 13 and 14, Figs. 5 and 6). Fig. 5 also shows the normal appearance of the muscular coat of the basilar artery immediately above and immediately below this level.

The posterior cerebral and superior cerebellar arteries themselves showed no abnormality.

The fusiform dilatation of the left vertebral artery was next examined. The intima here showed considerable thickening around the circumference of the lumen, and the muscle-tissue appeared thinned and stretched, although no defect in its continuity could be found at the level examined.

Discussion of the Cases.

1. *Clinical.* The syndrome upon which a diagnosis of ruptured basal aneurysm may be made has been so thoroughly described by Fearnsides (2), Symonds (3, 10), and Parker (6) that it is unnecessary to repeat it at length.

In Case No. II the first rupture was sufficiently severe to cause deep coma and death within two days, and an accurate diagnosis was therefore impossible, although it was clear that haemorrhage had occurred into the right side of the brain. The only clues as to the cause of the haemorrhage lay in the fact that the blood-pressure was hardly above normal and the heart was not obviously hypertrophied. It is the exception rather than the rule to find a markedly raised blood-pressure and signs of arteriosclerosis in these patients.

In Cases Nos. I and III the repeated 'cerebral attacks' with remissions offered strong presumptive evidence as to the diagnosis. The presence of blood in the cerebro-spinal fluid in Case No. I rendered this almost certain, though the possibility of a tumour into which haemorrhage had occurred had to be considered.

Two of the most constant symptoms in reported cases have been severe occipital headache and head-retraction. These generally occur a few days after the onset of the attack; they are probably due to blood gravitating into the posterior fossa of the skull and there acting as an irritant in a similar way to the inflammatory products in post-basic meningitis. For a similar reason Kernig's sign is often present in these cases. Both head-retraction and Kernig's sign were ultimately present in Case No. I, and when conscious her most constant complaint was of occipital headache. The diagnosis from meningitis obviously rests on an examination of the spinal fluid. An evenly blood-stained non-inflammatory fluid in a young or middle-aged patient probably means sub-arachnoid haemorrhage. If, after centrifugalization, the supernatant fluid has a yellow colour, the haemorrhage is probably of some little standing; this staining of the fluid also helps to distinguish pathological haemorrhage from that due to injury inflicted at the time of puncture. If there is, in addition, head-retraction, the diagnosis is rendered almost certain, provided that certain traumatic conditions can be excluded.

Other symptoms, such as the hemiplegia in Cases Nos. I and II, frequently give a clue as to the localization of the lesion. The subhyaloid haemorrhage in the right eye of Case No. III was of particular interest. Extravasations of this nature have been reported in several cases of cerebral aneurysm. Their appearance and significance are discussed in a paper by Leslie Paton (11). They are due to blood tracking from the subarachnoid space along the sheath of the optic nerve. As might be expected, they are most constantly met with in those cases in which the ruptured aneurysm is of the anterior cerebral, anterior communicating, or internal carotid arteries.

2. *Pathological.* These three cases have provided, in all, five aneurysms for section. Two of the patients were young (under 30), and in the third (aged 49)

there was, apart from the aneurysm, no evidence of atheroma in the cerebral blood-vessels.

In none of them would the aneurysms appear to have had a syphilitic or mycotic origin, nor, in the two cases in which we inquired for it, could any history of trauma be elicited.

The aneurysms in Cases Nos. I and II, and the two larger aneurysms in Case No. III, showed a similar histological structure which corresponded with the appearances described by Eppinger under the heading of 'congenital' aneurysms; that is to say, each consisted of two coats only and showed no trace of muscle-tissue in its wall.

In the case of the three most fully developed aneurysms—those which had ruptured—there were present in the wall of the sac well-marked degenerative changes: fatty and, in one case, calcareous. In the two smaller aneurysms in Case No. III such changes were comparatively slight. The smallest of the aneurysms in Case No. III, that on the basilar, appeared to show a very early stage in the development of these lesions. The serial sections obtained from it were therefore of particular interest. The essential change in this vessel was an atrophy and connective tissue replacement of the 'media' occurring at a single point in the circumference of the sac. It was associated with splitting of the elastic lamina and subendothelial hyperplasia of the 'intima', but seemed to me to indicate a primary lesion of the muscle-coat for the reasons already discussed.

The question which naturally arises is, What is the cause of this 'medial' change? Is it the result of infection? Histological evidence would suggest that it is not. The appearances suggested atrophy and fibrous replacement rather than an infective process, for there was no sign of lymphocytic nor plasma-cell infiltration of the vessel-wall.

Is it a manifestation of a 'juvenile' arteriosclerosis attacking essentially the middle coat of the cerebral arteries? That is a possible explanation; but if it be the correct one, the extraordinary constancy in position of these aneurysms is difficult to explain. In almost all cases, to quote Eppinger, they occur at the bifurcation or branching-point of vessels, and generally in the fork between the parent trunk and the origin of a branch. The sacs nearly always point in the direction of the blood-flow.

On the whole it would seem that the hypothesis of Eppinger of a congenital defect in the contractile tissues of the vessel-wall still offers the most likely explanation of their occurrence. It would seem to me that the histological findings in these cases do nothing to negative, but rather support this view.

I would suggest that the sequence of events may be as follows:

Firstly, that there is in these patients from birth a functionally weak or organically deficient point in the vessel-wall, this point occurring, as might be expected, where the muscle-fibres of the parent trunk change their direction in passing out to a branch.

Secondly, under the strain of the blood-pressure, particularly as this rises

with succeeding years, the defective 'media' stretches, producing a minute saccular dilatation, as was seen on the basilar artery in Case No. III. The body responds to this dilatation by a hyperplastic thickening of the intima as in the case of ordinary nodular sclerosis, according to the views of Thoma. The more the muscle-coat stretches, the wider does the defect become, the gap so produced being bridged by connective tissue cells and fibrous tissue. This fibrous replacement begins at the point of maximum convexity and spreads gradually to involve the whole sac.

Finally, we have the fully formed aneurysm as in Cases Nos. I and II, consisting only of adventitia and enormously thickened intima, the muscle-coat of the parent vessel ending more or less abruptly at the point of dilatation. It has been suggested that indirect trauma may play a part in the formation of these aneurysms (Hedinger (12)). In the cases under consideration no history of trauma was obtained, but in a certain proportion of reported cases it appears that injury to the head has acted as a factor in determining rupture, if not the formation of the sac.

Eppinger, in first postulating a congenital basis for these aneurysms, suggested that there was in these patients an inherent defect in the elastic and muscular elements of the vessel-wall. The sections made from these cases would suggest that the defect is primarily a muscular one, for in the case of the smallest and apparently 'youngest' aneurysm the internal elastic lamina, though swollen and split at the site of the lesion, appeared to be continuous around the circumference of the sac except in one very limited area at the point of widest muscular defect. Even in the larger, fully formed dilatations, elastic tissue could be traced for some distance into the aneurysmal wall. It would seem to me, therefore, that the muscle-coat is probably the first to break, the elastic lamina afterwards being fragmented and stretched, finally to give way at a later period. Again, it is possible that the fragmentation of the elastic layer may result from impaired nutrition of this part of the wall due to the hyperplastic thickening of the 'intima'. This has been suggested as its cause in ordinary nodular sclerosis, and it may hold good also in the case of cerebral aneurysms. The degenerative (fatty and calcareous) changes met with in the walls of the larger aneurysms would appear easy to explain on similar grounds, partly because of the great thickness of the 'intima', and partly because the blood in the lumen is separated from the vessel-wall by a mass of laminated blood-clot.

It is of interest to note that in 1894 W. L. Dickinson (13) showed to the Pathological Society two specimens of abdominal aneurysm associated with congenital hypoplasia of the aortic wall. His patients were aged 29 and 30 respectively, and in one of them multiple aneurysms were present. Unfortunately there is no record as to the condition of the cerebral arteries in these cases.

An important point in favour of a congenital basis for cerebral aneurysm is the fact, previously mentioned, of the occurrence in several cases of lesions of this nature in patients with coarctation of the aorta. Where one congenital abnor-

mality exists it is by no means uncommon to find others. Against this may be objected the fact that in patients with aortic coarctation, it is common to find an abnormally high blood-pressure in the vessels to the head, neck, and upper extremities, and this in itself might be adduced to account for the formation of aneurysms in the brain.

Summary.

1. In this paper are described three cases of 'spontaneous subarachnoid haemorrhage' due to rupture of saccular aneurysms upon branches of the circle of Willis.

Two of the patients were young (aged 21 and 30 respectively). The third was aged 49, but she showed comparatively little evidence of arteriosclerosis.

In each case a syphilitic or 'mycotic' origin for the aneurysms could practically be excluded, both on clinical and pathological grounds.

In the two cases in which we inquired for it, no history of old or recent trauma to the head was elicited.

2. Detailed histological examination has been made of the wall of each of the five aneurysms found in these three cases; a report is given of the serial sections through a vessel showing what appeared to be a very early stage in the production of aneurysm.

The larger sacs showed the microscopical changes described by Eppinger under the heading of 'congenital' aneurysms. The smallest (youngest) aneurysm showed a localized defect in its muscular and elastic coats, which would seem to be consistent with Eppinger's hypothesis of a congenital basis for these lesions.

3. One of the patients who form the subject of this paper showed, *post mortem*, in addition to three cerebral aneurysms, cardio-vascular maldevelopments in the form of coarctation of the aortic isthmus, a bicuspid aortic orifice, and fenestration of the mitral cusps.

Reference is made to three other cases from the literature, in which the rare condition of coarctation of the aorta has been associated with the presence of one or more aneurysms in the brain.

This association lends additional support to the view that aneurysm of the cerebral arteries may, like the aortic deformity, have a congenital basis in local maldevelopment of the vessel-wall.

My thanks are due to Sir Frederick Andrewes for kindly examining and offering advice upon my sections. I am also indebted to the Medical Research Council for the grant which enabled the histological part of the work to be carried out.

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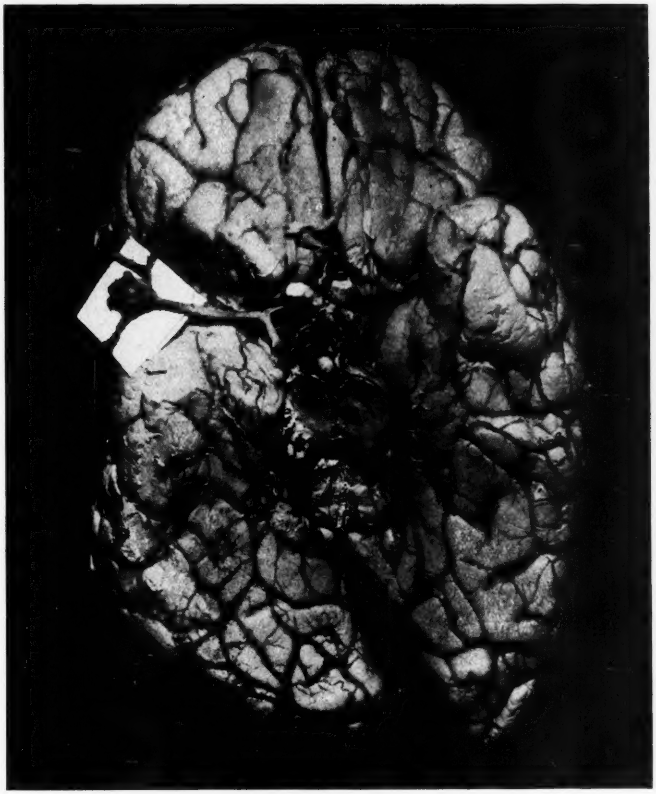

FIG. 1. Case I. To show position and appearance of the aneurysm, which had ruptured at its distal extremity. The right middle cerebral artery and the sac were surrounded by a mass of blood-clot which has been removed, together with a portion of the temporo-sphenoidal lobe.

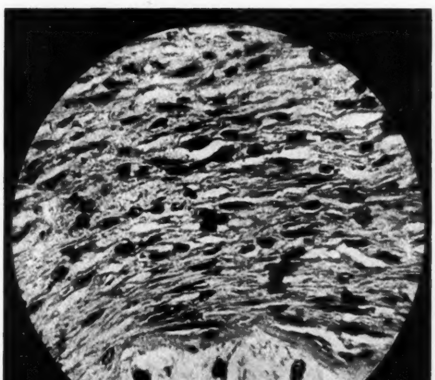

FIG. 6. Case III. High-power photograph of defective area of 'media' shown in the middle picture, Fig. 5, to show connective tissue replacement of muscle-coat.

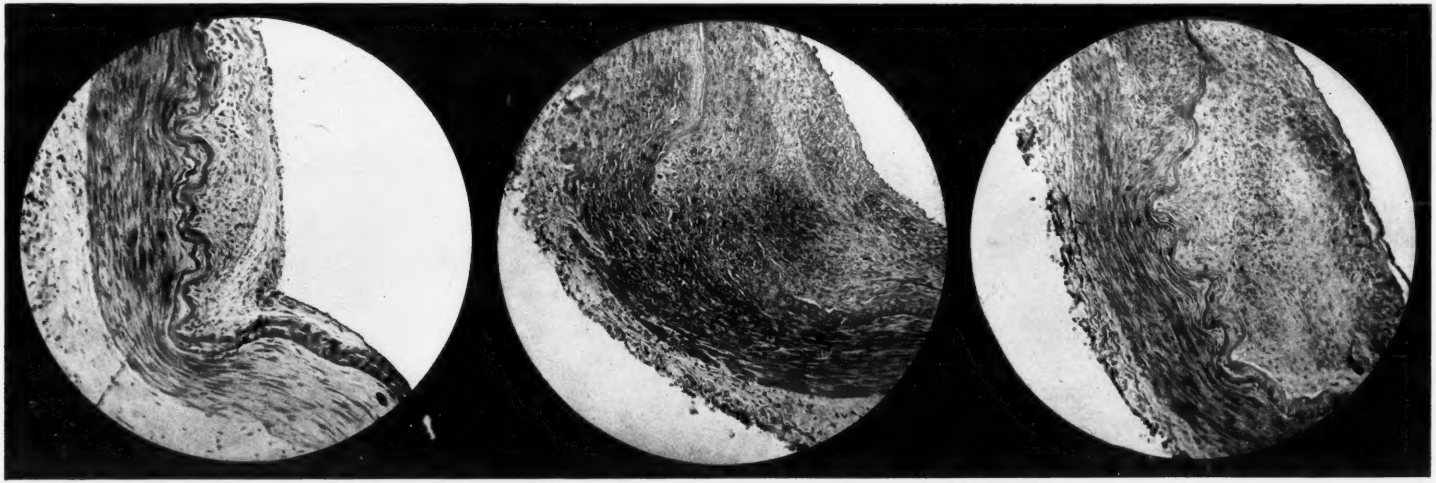

FIG. 5. Case III. Photomicrographs of the saccular dilatation shown in Fig. 4. The middle photograph shows the localized defect in the muscular and elastic coats referred to in the text; those on the left and right respectively show the normal appearance of the muscle-coat above and below this level; at all three levels there is marked intimal thickening and splitting of the elastic lamina.

RAT-BITE FEVER: A STUDY OF THE EXPERIMENTAL DISEASE, WITH A CRITICAL REVIEW OF THE LITERATURE[1]

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Introduction.

THOUGH rare in Europe in contrast to its more frequent occurrence in the East, rat-bite fever has attracted particular interest since the demonstration of the specific organism—*Spirochaeta morsus muris* (or *Spirillum minus*). The discovery of this spiral organism in 1916 by Futaki and his co-workers (36 *a*) revealed a unique type of pathogen and opened the way to further studies of its biology and pathogenesis in man and animals and of the sources and modes of infection. Such studies have shown how the specific organism may occur in the blood of wild rats and mice, producing a natural epizootic infection, and it is of particular interest that the bite of certain other animals, e.g. ferrets, may also occasionally convey the infection to the human subject. It may be recalled here that an organism apparently identical with the *Spirochaeta morsus muris* was described in 1887 by Carter in the blood of a wild rat and designated by him '*Spirillum minor*'.

In 1926 a strain of *Spirochaeta morsus muris* was transmitted to laboratory animals from a case of rat-bite fever in the Royal Hospital for Sick Children, Edinburgh, and the writer was afforded the opportunity of carrying out with this strain an extended study of the experimental infection which forms the subject of this communication. The experimental disease in various animals has been carefully investigated and compared with rat-bite fever in the human subject; and interesting differences in pathogenesis towards different species have been elicited. A striking and important result has been the apparent analogy between the experimental disease in certain animals and syphilitic infection in the human subject. This study has therefore rendered available a method of reproducing easily and certainly in the laboratory infections which in their pathology closely parallel the various essential stages of syphilitic disease. It is noteworthy in this connexion that Ehrlich, in his classical experiments on the chemotherapy of spirochaetal infections leading to the discovery of salvarsan, used the *Spirochaeta laverani*, which is probably identical with the *Spirochaeta morsus muris*.

[1] Received March 5, 1928.

The biology of the causative organism has also been studied. In biological characters it is more allied to the spirilla than to the true spirochaetes. On the other hand, in its pathogenesis, and also in regard to the chemotherapy of the infection in man and animals, the organism appears to bear a close relationship to certain pathogenic spirochaetes.

Historical.

While recognized and studied in old Japanese times, the disease was first clearly described by Katsura in 1892, in his Japanese text-book of surgery; in the following ten years fifteen cases were reported in the Japanese language, but it was not until 1902 that Miyake (1) gave the first description of the condition in a European language and applied to it the name 'Rattenbisskrankheit' (Japanese, *sodoku*; *so* = rat, and *doku* = poisoning).

Miyake's paper led to the recognition of rat-bite fever as a clinical entity in Europe and America, but previously a number of descriptions of 'poisoning from a rat-bite' had been published in both continents. The earliest of such communications was by Wilcox (2) (1840) in America, and between this date and Miyake's communication thirteen cases in all had been described in that country by Watson (3) (1840), Gilliam (4) (1868), Packard (5) (1872), Earle (6) (1872), Banker (7) (1886), Cook (8) (1886), and Evans (9) (1902). The first descriptions of the disease in Europe were by Millot-Carpentier (10) (1884) and Pena y Maya (11) (1885) in France and Spain respectively. From the accounts given by the above authors it seems almost certain that they were dealing with rat-bite fever as described by Miyake.

Review of the Clinical Features of the Disease.

The disease usually commences within thirty days after the bite, with a rigor followed by a rise in temperature and in pulse and respiration rates. The earlier Japanese authors, however, claimed that the incubation period might be as long as two years. The bite wound usually heals by first intention; in most cases, about the time of onset, pain is felt in the scar, and the surrounding area becomes swollen and oedematous; later, vesicles form at the position of the bite and in many cases the wound ulcerates, the ulcer presenting a clean surface, indurated edges, and a serous discharge (in which the causative spirillum is frequently demonstrable), and resembling the scrotal lesions of the experimental disease in the guinea-pig (*v. infra*). Arkin (12) (1920) and Adams (13) (1925) lay stress upon the resemblance of this ulcer to an extra-genital chancre. It is worth noting that in the true spirillary *sodoku* pus is not formed—pus formation apparently indicates a mixed infection or an infection with organisms other than the spirillum.

Coincident with these changes in the wound, lymphangitis develops, accompanied by a swelling of the regional lymph glands, which are at first soft in

consistence, but later become firm, though always remaining discrete and not adherent to surrounding structures.

The temperature soon returns to normal, but after a variable interval—usually three to four days—rises again, with or without a rigor, only to fall after two or three days. This intermittent course usually continues for some months, a spontaneous cure ultimately resulting, but may be prolonged for years, e.g. four years in the case recorded by Corinaldesi (14) (1924) and eight years as reported by Surveyor (15) (1913).

During the apyrexial intervals the patient usually feels quite well and presents few or no symptoms except the local changes and the lymphadenitis. The febrile periods are accompanied by other symptoms, e.g. muscle and joint pains, vertigo and headache, and often by the appearance of the characteristic rash.

The rash, present as a rule only during the pyrexial attacks, is a maculo-papular eruption of a reddish-purple colour occurring in patches from the size of a pea up to that of the palm, regular in outline, indurated and slightly elevated above the surface of the skin, disappearing only on heavy pressure, and usually unaccompanied by pain, though a burning sensation may be complained of. It is generally said that the rash does not involve the head, palm, sole, or mucous membranes; it has, however, been described as involving these regions—the face by Herzfeld and Mackie (16) (1926), and the throat mucosa by Collier (17) (1924) and Giglioli (18) (1927).

An urticaria towards the end of the disease is described by Miyake (1) and by D'Halliun and Fievez (19) (1918).

The fall of temperature to normal is almost invariably accompanied by sudoresis.

The lymphadenitis increases until the glands may be as large as a hen's egg, and extends until all the superficial glands are palpable.

In a favourable case the attacks of fever occur at longer and longer intervals, and are of less and less degree, and ultimately cease, while the glandular enlargement disappears.

The ulcer at the position of the bite heals, leaving a bluish-red patch, which may persist for years.

Certain symptoms and signs which are not constant, or are present only in the more severe cases, may now be briefly dealt with.

Circulatory System. In long-standing cases some degree of anaemia is very frequently present, along with polynucleosis and a mild eosinophilia. A haemic murmur may be present—Dick and Rutherford (20) (1913).

Respiratory System. Is usually very little affected, though in some cases slight bronchitis with slimy expectoration, and rarely dyspnoea, have been observed. Pleurisy has been reported—O'Carrol (21) (1912).

Alimentary System. In long-continued cases constipation is usual. The tongue shows a yellowish-brown coating, and in one case—Burton-Fanning (22) (1921)—was much swollen. Abdominal pain occurred in Cruickshank's (23) case

(1912); gastro-enteritis was observed by Annibale (24) (1920), Carpentier (10), Pena y Maya (11), and Cook (8). Icterus has been recorded in one case—Fulghieri's (25) (1925).

The spleen is usually not involved; however, splenic pain has been recorded by Dick and Rutherford (20) (1913), and in cases described by Miura and Toriyama (26) (1897) and Burton-Fanning (22) (1921) the organ was definitely enlarged.

Genito-urinary system. In mild cases there may be no involvement of the kidney, but in cases of any severity a toxic nephritis is common, the urine being diminished in amount and containing albumin and casts. The diazo reaction may be positive.

Epididymitis was present in one case of Burton-Fanning's (22).

Nervous system. Is usually affected, especially during the attacks of fever, when headache, a heavy feeling of the head, tinnitus, vertigo, delirium, stupor, or coma may occur. Anopsia has been observed—Ebert and Hesse (27) (1925). Muscular tenderness is a practically constant symptom—sometimes, indeed, the muscles are indurated—Grenet and Lehucher (28) (1918). The tendon reflexes may be increased, diminished, or absent; anaesthetic or paraesthetic areas on the extremities are common; patches of hyperaesthesia may occur anywhere on the body. Conjunctivitis, with or without chemosis conjunctivae, has been seen —Frugoni (29 *b*) (1912).

Skeleton. Periostitis and perichondritis may be present—Ebert and Hesse's case presented perichondritis of the rib cartilages and spondylitis, but, in view of the occurrence of pus containing a leptothrix, these lesions may not have been due to the specific spirillum. Joint pains, particularly mentioned by Mauriac (30) (1918), are common.

The Wassermann reaction is positive in about 50 per cent. of cases—Blum and Clement (31) (1925).

Ten per cent. of untreated cases die, but in cases treated by salvarsan the mortality is negligible.

While the preceding description may be taken as applying to the majority of cases, Miyake describes, in addition, an apyrexial form, in which the nervous symptoms are severe and which is frequently fatal, and an abortive form, in which only one or two febrile attacks occur, and from which recovery is rapid.

Morbid histology. Microscopic examination of the local lesion has been made by Proescher (32) (1911) and by Delamare and Mouchet (33) (1923), and of the regional glands by Delamare and Mouchet (33) (1923) and by Herzfeld and Mackie (16) (1926). The descriptions, except that of Proescher, do not differ appreciably from that of corresponding lesions in the guinea-pig; as Proescher observed a peculiar organism in his specimens, his description is not suitable for comparison.

Post-mortem appearances. Complete autopsies have been performed by Miura and Toriyama (26) (1897), Kaneko and Okuda (34) (1917), and Blake (35) (1916). Omitting changes due to the age of the subjects, their findings may be

summarized as follows : (1) General marasmus, (2) parenchymatous degeneration of heart, liver and kidneys, (3) catarrhal gastroenteritis, (4) catarrhal cystitis, (5) meningeal hyperaemia and oedema, (6) lymph glands hyperplastic with dilated sinuses, (7) hyperaemia of suprarenal cortex, of spleen and kidneys, (8) hyaline degeneration of central arteries of Malpighian bodies in the spleen. Such findings agree, both macro- and microscopically, with those in experimental guinea-pigs.

Geographical Distribution.

Between Miyake's publication and the definite establishment of the spirillary origin of the disease by Futaki and co-workers (36 *b, c, d*) (1917), many cases were reported in Europe and America, the two earliest reports being those of Horder (37) (1909) in England, and Proescher (32) (1911) in U.S.A. Cases have by now been reported from almost every country, including Britain, France, and Italy. It is of interest to note that King (38) (1914) has reported a case infected from a ship rat. Out of 49 papers published since 1918, dealing with the disease, the demonstration of the spirillum is mentioned in 29. A list of cases arranged according to countries, in chronological order, is appended to the bibliography.

Bacteriology of Disease.

Before the description of the causative spirillum by Futaki, Takaki, Osumi, and Taniguchi (36 *a*) in 1916, a number of organisms had been described as occurring either in the wound or in the blood, or in both: thus, Ogata (39) (1908) described a sporozöon in the wound ; Middleton (40) (1910) a diplococcus in blood-smears ; Proescher (32) (1911) a peculiar bacillus in wound and glands ; Schottmüller (41) (1914), Blake (35) (1916), Tileston (42) (1916), Litterer (43) (1917), and Tunnicliff and Mayer (44) (1918), a streptothrix. The dominant etiological role of the spirillum has been confirmed by numerous observers since 1916. It is of interest to note that prior to the work of Futaki a spirochaetal origin had been suspected by Hata (45) (1912) and Oda (46) (1915) in Japan, Surveyor (15) (1913) in India, and Crohn (47) (1915) in the U.S.A., and that on this hypothesis cases had been successfully treated with salvarsan and its homologues.

Since 1917 organisms other than the spirillum have been found in a few cases—a coliform organism isolated by blood-culture in a case of Solly's (48) (1919), which was, however, cured by neosalvarsan ; a streptococcus in lymph glands by Douglas, Colebrook, and Fleming (49) (1918), and by Nixon (50) (1914) ; a 'leptothrix' by Thorpe (51) (1925) ; a streptothrix by Ebert and Hesse (27) (1925), and an organism not unlike that described by Blake (35) (1916) isolated by blood culture in the case from which the strain of spirillum studied in this investigation was derived.

It is probable that the streptococci and coliform organisms reported, and the organism described by Mackie (16) (*v. infra*), were merely secondary invaders,

possibly from the patient's intestinal tract. Proescher's 'bacillus' only stained after mercuric chloride fixation and by Giemsa's stain, was not cultivable, and his results in animals were very similar to those obtained with the spirillum; it is just possible that he was really dealing with the specific spirillum.

The description given by Tileston (42) of a 'streptothrix' in the blood, which he was unable to cultivate, suggests that he may have been misled by the 'pseudo-spirochaetes' which are often present in febrile and wasting conditions (see Thomson (52) (1923)).

In considering the cases from which a streptothrix or leptothrix has been derived, the following facts are of importance: (1) In all but one or two of these cases *pus* was present—suppuration does not seem to occur in true *sodoku*; (2) in streptothrix pyaemia, as described by Mandelstam and Kalinin (53) (1926), who indeed refer to Blake's and Schottmüller's cases under this heading, an intermittent fever as in *sodoku* occurs, and the remaining clinical features are very similar; (3) a streptothrix, which in culture developed leptothrix-like filaments, has been demonstrated in a form of broncho-pneumonia of rats by Tunnicliff (54) (1916); (4) the transmission of other diseases by the bite of rats has been recorded, e.g. sporotrichosis by Jeanselme and Chevalier (55) (1910) and Maxwell (56) (1913), cutaneous tuberculide by Dick and Rutherford (20) (1913), and a filterable virus septicaemia by Brodin and de la Rivière (57) (1926).

From the foregoing, it is not unreasonable to presume that a strepto- or leptothrix infection may be transmitted to man by the bite of a rat. The further inference may also be drawn that in every case of intermittent fever following a rat-bite, the possibility of a streptothrix infection being present, either alone or along with spirillosis, must be borne in mind, especially if salvarsan treatment is not proving satisfactory.

In the cases in which the spirillum has been demonstrated, this organism has been found several times by direct examination of the serum from the wound or from a patch of the eruption and occasionally in smears from regional lymph glands; in only one—Costa and Troisier (58) (1918)—have spirilla been found directly in the peripheral blood, though most of the human strains have been derived by blood inoculation.

Though called rat-bite fever, the disease has followed the bite of cats, ferrets, and in one case of a dog—Cazamain (59) (1921). The identity of cat- and rat-bite fever was proved by Yamada (60) (1917), Sano (61) (1917), Izumi and Kato (62) (1917), Kitagawa (63) (1917), and Mooser (64 *b*) (1925). The disease has also been transmitted by the scratch of a cat—Yamada (60) (1917) and Sano (61) (1917)—in which transmission was probably due to mechanical transfer, and in one case, Boidin (65) (1922), by the eating of a raw rat.

Spirochaeta morsus muris or *Spirillum minus*.

The strain of spirillum (*Spirochaeta morsus muris* or *Spirillum minus*) with which the experimental work of this paper has been carried out was isolated

by Professor Mackie from a case under the care of Miss Herzfeld, F.R.C.S. Ed., at the Royal Hospital for Sick Children, Edinburgh; the case has already been described in the *Edinburgh Medical Journal* of October, 1926.[2] The following is a summary of the history:

In December, 1925, the patient, a boy aged 5, was bitten on the forehead while asleep. The wounds healed without any trouble. A fortnight later he appeared unwell and a swelling, which subsided after fomenting for a few days, appeared in the region of the bite. A few days later the regional lymph glands were observed to be enlarged. About a month after the bite, he was feverish, and the brow and forehead were markedly swollen. He was admitted to hospital on the 14th day of the disease. While in hospital, he had four pyrexial attacks —on the 19th, 25th, 29th, and 36th days of his illness. Between these attacks the oedema of the face diminished only to increase anew as the temperature rose. Though on one occasion he had a temperature of almost 105° F., there was extremely little general disturbance. As the enlargement of the cervical glands was still increasing, however, a number of them were excised on the 49th day. Four days and again ten days after operation, doses of 0·05 and 0·10 grm. novarsenobillon were administered, and the case was then discharged, the swelling and oedema of the face having quite disappeared.

Unsuccessful attempts were made to demonstrate the spirillum in peripheral blood, urine, and exudate from the oedematous area, and from a patch of erythema on the face. When the excised lymph glands were examined, suspicious forms were seen and, upon inoculation of gland emulsion into two guinea-pigs, spirilla appeared in their blood after incubation periods of 19 and 37 days.

This strain has been carefully investigated as regards its various biological characters.

Morphology. The spirillum may be studied either by dark-ground illumination, when it appears as a rapidly moving refractile wavy organism, or in Romanowsky-stained preparations, in which it is coloured a deep violet. It also stains by aniline dyes, e.g. weak carbol-fuchsin, gentian violet, methylene blue. It is Gram-negative. Silver impregnation methods, e.g. Fontana's, are not so satisfactory as Romanowsky staining, inasmuch as not all the organisms in a film are impregnated; also the fixative causes the body to swell, its waves thus becoming indistinct.

The spirillum is usually described as forming a spiral, but careful observation under dark-ground illumination shows—as first noted by Ruys (81)—that the windings lie in one plane. In length, non-dividing forms measure from 1·5 μ to 10 μ, exclusive of flagella, with approximately one wave per μ.

The waves are regular and about 0·8 μ in amplitude. The ends of the organism may be either blunt or pointed. Movements are rapid and more or less in a straight line except when diverted by other objects—such as red blood-cells—when a to-and-fro movement occurs, in which first one and then the other end of the body is anterior and rotation takes place around the longitudinal axis. Very rarely the parasite may be seen apparently rotating about the centre of its

[2] A communication has also been published by Mackie and McDermott (1926) on the bacteriological investigation of the case (*Journ. of Path. and Bact.*, 1926, xxix. 493).

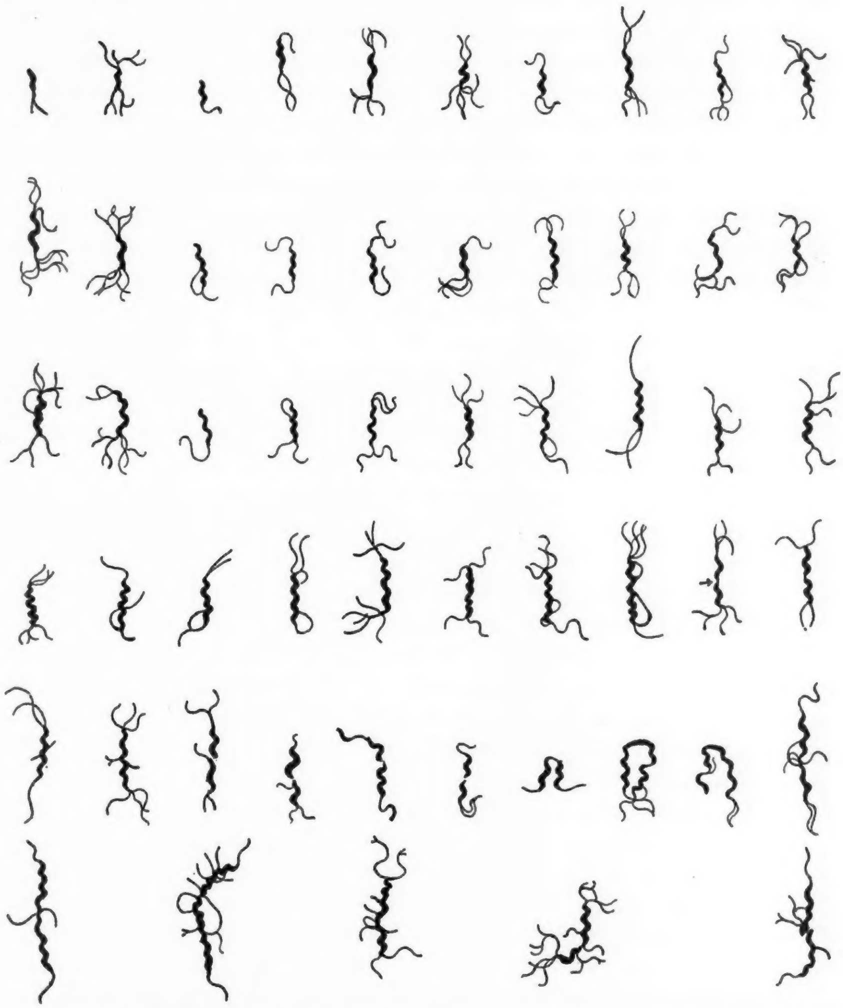
body. There is no undulation. In non-dividing forms there is no bending of the body in free movement; this only occurs when an obstruction is encountered, and even then is only slight and recovered from as soon as the body is free to straighten again. Bending of the body, described by Mooser (64 *a*) (1924) and stressed by him as tending to place the organism among the Treponemata, occurs only in dividing forms at the point of subsequent division, where for a time constriction is hardly noticeable and flagella may not be present. Motility is retained for over 24 hours at room temperature in blood sealed from the air Unfortunately, bright light soon inactivates the organism; hence observations on a single living specimen can only be carried out for a few seconds, after which it first becomes immobile and then swells until its waves disappear.

Division is transverse; a slight constriction appears, which subsequently deepens, becomes drawn out into a fine thread (staining more lightly than the body) as the young organisms draw apart, and ruptures as they separate. Flagella may be formed at the point of division before separation of the new individuals, and give rise to the appearance of lateral flagella; sometimes, however, this does not occur, and thus occasional young forms are met with having flagella of normal length only at one end—the other end being either devoid of flagella or having only short ones. Usually fission is binary; division into three has been fairly frequently observed, however, and once an organism dividing into four was seen. U and Y forms are explicable by flexion at a point of transverse division, and it is not necessary to postulate longitudinal fission.

The flagellum itself merits attention. Normally both ends possess flagella. By dark-ground illumination these are seen to be in rapid movement, streaming out from the rear, while those in front are trailing backwards beside the body; the rapid movement prevents a count of their number, and when partially slowed they appear more often as a single, fairly thick structure, though sometimes two and even three may be seen by dark-ground.

It is only when stained that the flagella can be satisfactorily studied. They may stain with Leishman's stain, but usually only faintly; the best method for their demonstration is that described by Adachi (66) (1921), viz. fixation for 30–60 seconds by osmic acid vapour over a solution: osmic acid 1 grm., distilled water 100 c.c., 5 per cent. mercuric chloride 10 drops; staining for several hours—usually overnight—in Giemsa's solution, diluted 1:10, to each 10 c.c. of which 0·6 c.c. of 1 per cent. potassium carbonate has been added. The results are always uncertain. In such preparations all the spirilla except a few immature forms possess one or more flagella at both ends. The flagella number from 1 to 7 and, approximately, vary in thickness inversely as their number. The ends of the organism may be pointed or blunt; if blunt, there are always more flagella than one; if pointed, there may only be a single flagellum. There is no relation between number of flagella and size of body, nor between the number of flagella at one end and the number at the other. These flagella are 7–8 μ long, and wavy, frequently continuing the direction of the body-waves for one or two turns, but

gradually becoming almost straight. Branching of the flagella into two or three is frequent, but reunion of these branches or of adjacent flagella, when seen, is probably apparent only (see below).



Series of freehand drawings from Adachi-stained films of blood from an infected guinea-pig, to show variations in morphology of organism, and in form and number of its flagella. The last two organisms in the fourth row and those in the fifth and sixth rows are in different stages of transverse division.

After fixation with methyl alcohol and Giemsa staining, and in Fontana-stained preparations, the flagella appear thick and single.

Cultivation. Futaki and his co-workers (36) (1917) claimed to have cultivated the spirillum in Smith-Noguchi and Shmamine (67) media, but all attempts by other observers to repeat the culture have been unsuccessful. The forms

described by them in culture differ so substantially from the free-living organism that, as pointed out by Robertson (68) (1924), it would seem that either they had cultured some other spiral organism or were misled by the appearance of fibrinous threads which develop in these and similar media.

Joekes (69) (1925) claims to have cultivated the organism in symbiosis with a Gram-negative bacillus in a special medium, but I have been unable to obtain similar growths. Inoculations of citrated guinea-pig blood containing many spirilla per field of the dark-ground microscope were made into a variety of media, including those suitable for the growth of spirochaetes, leptospiras, trypanosomes, vibrios, and entamoebae, in addition to the common media. All media were incubated at room temperature and at 30° C., and examined frequently by dark-ground illumination. In none was growth observed. In citrated blood or in broth, the organisms survived for 24–48 hours at room temperature or at 37° C.

Experimental Inoculation.

Experimental infection has been produced in mice, white rats, guinea-pigs, rabbits, cats, ferrets, and *Macacus rhesus*.

Mice. A large number of experiments with these animals have been carried out. They were readily infected by subcutaneous inoculation, and, after an incubation period of 3–12 days, the organism could be found in the peripheral blood. A polymorphonuclear leucocytosis was usually noted about the fourth day and subsided 2–3 days before the appearance of the spirilla. The organisms rapidly increased in number, but after about a fortnight they became progressively less numerous and ultimately could not be demonstrated by microscopic examination. Relapses, however, occurred at irregular intervals; and the spirilla were demonstrable by inoculation tests up to 6½ months after infection. The mice remained apparently in perfect health, and even after prolonged infection showed on autopsy only a slight enlargement of the spleen. In the tissues the organisms were never found in greater number than could be accounted for by the blood present.

As filterable forms were stated to exist in the spleen of the mouse by Salimbeni, Kermorgant, and Garcin (71) (1925), their experiments were repeated, but with negative results.

A newly born mouse from an infected mother was killed and ground into an emulsion which was used to inoculate a number of healthy mice, but none of them developed the disease. Salimbeni and co-workers (71) (1925) claimed to have demonstrated hereditary transmission, but this was not the case in the experiments of Worms (72) (1926) or Abe (73) (1924).

Rats. In all, 14 animals were inoculated. Of these, 13 showed uniform effects; one animal proved naturally refractory. In 4–14 days the spirilla appeared in the blood, increased in number to a maximum, never, however, being so numerous as in mice, and then diminished and disappeared, though they were

demonstrable in small numbers for about four weeks; subinoculation of other animals with blood after four months gave negative results.

Mooser (64 *a*) (1924) first demonstrated the occurrence of keratitis, conjunctivitis, and iritis due to the spirillum after $3\frac{1}{2}$–$4\frac{1}{2}$ months, but did not describe any other pathological changes.

When the observation of experimentally infected rats was continued—and this applied also to experiments with the allied *Spirochaeta laverani*[3]—it was seen that the rats after about $3\frac{1}{2}$ months became less active; keratitis with iritis, or conjunctivitis, developed, and death resulted usually after nine months. On autopsy at this stage the lungs presented numerous round white nodules of all sizes up to that of a hazel-nut, which on section were found to contain necrotic matter well encapsuled by fibrous tissue; the lymph glands, especially those in the mediastinum, also contained these nodules: these changes were met with as early as the fourth month. In some animals similar nodules were found in various organs, e. g. liver and spleen. The presence of spirilla was demonstrated by inoculation of necrotic material from the lesions into mice and guinea-pigs. Tuberculosis and other infections were excluded by appropriate inoculation tests. These lesions commenced apparently in the lymphoid tissue of the particular organ with hyperplasia and endothelial cell proliferation; later, necrosis occurred in the centre of the hyperplastic masses. The lung lesions showed a close resemblance to those described in a case of human pulmonary syphilis by Rukstinat (74) (1926) and by Warthin (75) (1918).

The serum of an infected rat $4\frac{1}{2}$ months after inoculation, when diluted up to 1 in 16, was found to immobilize the spirillum in mouse blood; normal sera showed no similar effect. The heated (55° C.) serum of the animal referred to above also gave a positive Sachs-Georgi flocculation test, which is not a normal attribute of heated rat serum.

The disease in rats presents the following successive phases:

An incubation period; a 'primary' inflammatory lesion, the organisms being localized to the lesions and regional lymphatic glands at this stage; a 'secondary' stage, during which the organisms are present in the blood; a latent stage, in which the blood is free from spirilla and there are no obvious lesions; a 'tertiary' stage, with the above-described 'gummatoid' lesions.

Thus the course of the disease and its manifestations in this animal present an interesting analogy with syphilis in the human subject.

Guinea-pigs. Careful observations were made in thirty-two experimentally infected animals. About eight days after subcutaneous injection an inflammatory lesion developed which in many cases ulcerated. In the serous discharge from the ulcer numerous spirilla were demonstrable. The formation of an ulcerated local lesion occurred most frequently when inoculations were made in the scrotum or labium majus, either by subcutaneous injection or by application of the infected material to an abraded surface. In histological structure the ulcer corresponded closely to the descriptions given by Proescher (32) (1911) and Delamare and

[3] This strain was obtained from Professor Browning of Glasgow.

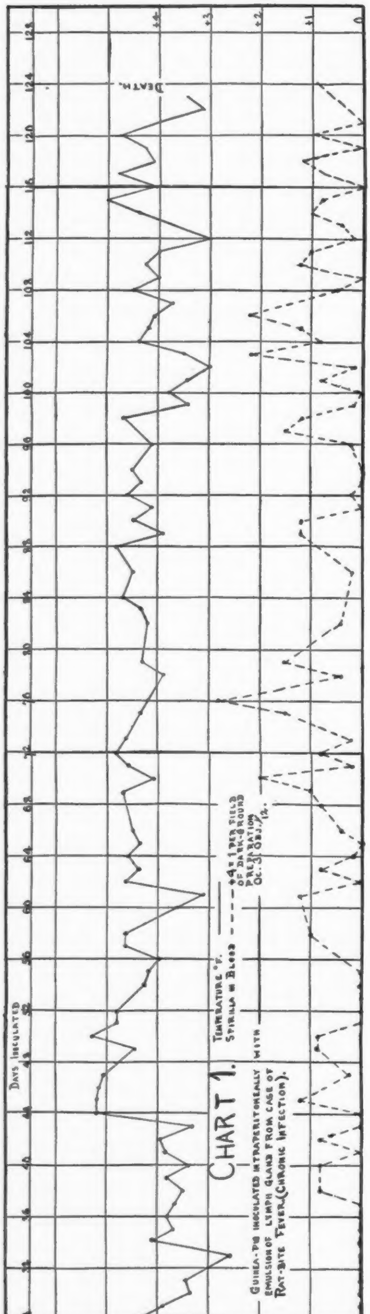


CHART 1.
Guinea-pig inoculated intraperitoneally with emulsion of lymph gland from case of Rat-bite Fever (Chronic Infection).
Temperature °F.
Spirilla in Blood
Days Inoculated
Death.

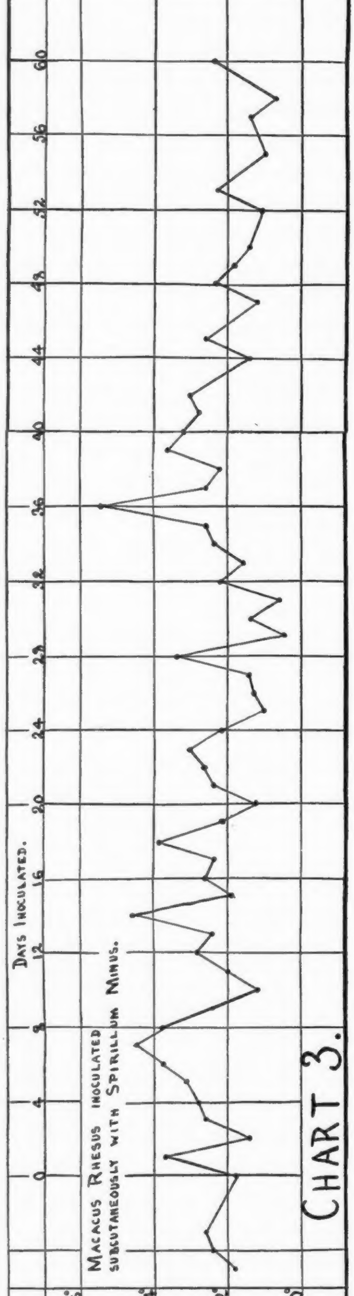
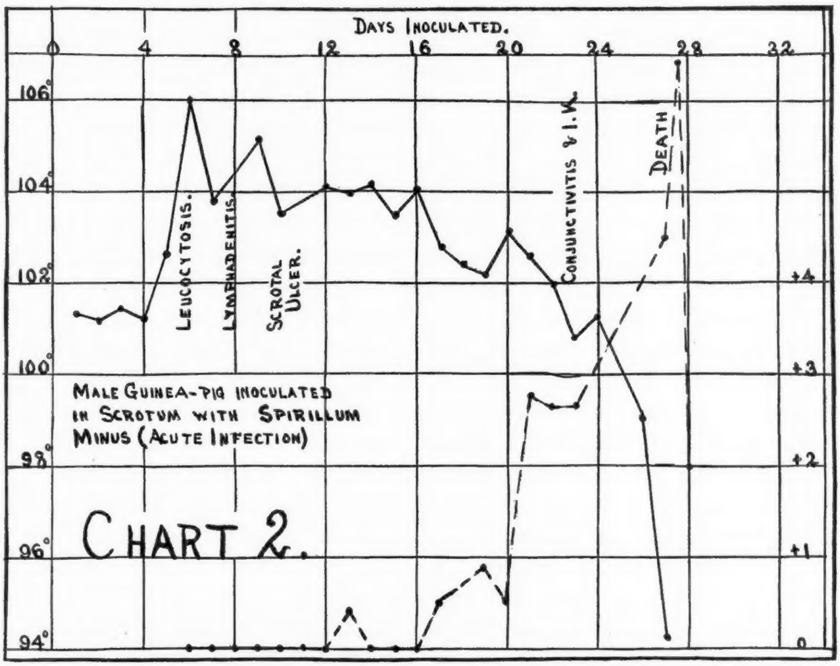


CHART 3.
Macacus Rhesus inoculated subcutaneously with Spirillum Minus.
Days Inoculated.

Mouchet (33) (1923) of the local lesions in man, and has been referred to in experimental rat-bite fever by Ishiwara, Ohtawara, and Tamura (91) (1917).

The local lesion was accompanied by enlargement of the regional lymph glands, which showed changes comparable to those in the human disease (*vide supra*). Spirilla were demonstrable in stained smears of these glands, even before their appearance in the blood.



The disease ran in most animals a typical and fatal course. Within twenty-four hours of inoculation the animals showed pyrexia (possibly due to the foreign protein of the blood inoculum), but the temperature rapidly returned to normal; it rose again in 2–3 days and thereafter most guinea-pigs developed an intermittent pyrexia—102° to 104° F. or over—until just before death, when the temperature fell to subnormal.

The appearance of spirilla in the peripheral blood was preceded by a transient, but often very marked, polynucleosis. The organisms were at first scanty in number, but increased gradually, with many fluctuations, to a degree which was fairly well maintained until shortly before death, when, coincidently with the fall in temperature, they increased very rapidly in number. This increase in the blood continued *post mortem* for about twenty-four hours. This is of interest when considered with the analogous findings of Kratzeisen (76) (1923) in the case of *Treponema pallidum* in the human cadaver.

In the first two animals inoculated the incubation periods, as already noted, were 19 and 37 days, and death ensued after 62 and 124 days respectively.

After passage, the incubation period averaged 9 days—extremes being 5 and 13 days—while the average duration of life after infection was 28 days (Charts 1 and 2).

Conjunctivitis and keratitis developed in the majority of the animals, and in the copious mucoid discharge spirilla were demonstrable. In those animals in which the infection was prolonged, the eye lesions healed and relapsed several times. Special features noted in these animals at autopsy which may be commented on were: (1) Interstitial myocarditis with nodules of perivascular and interstitial infiltration by mononuclear cells along with plasma-cells, polynuclear leucocytes, and fibroblasts; (2) hyperplasia of both lymphoid and endothelial cells in the lymph glands; (3) endothelial cell proliferation in the spleen with progressive fibrosis.

A minority of the experimental animals exhibited atypical infections, e. g. delayed onset of pyrexia, late appearance of the spirilla in the blood, development of keratitis before organisms were demonstrable in the blood; these are of interest, since they correspond to types of infection reported as characteristic of different strains that have been described. An atypical result of special interest was noted in one animal (inoculated from an infected monkey—*v. infra*), which showed no noteworthy symptoms and no spirilla in the blood, and was apparently quite healthy for 3½ months with the exception of slight enlargement of the glands related to the site of inoculation. These glands were excised and inoculated into a mouse, which developed the typical infection. In this guinea-pig apparently the infection assumed a 'latent' form. Such latent spirillosis was described by Mooser (64 *c*) (1926), but has not been noted by other workers.

Serology.

The serum of infected guinea-pigs at a late stage of the illness, in dilutions up to 1 in 8, was capable of immobilizing the spirilla in mouse blood in one hour—this effect was exerted towards both the homologous *Spirillum minus* and a strain of *Spirochaeta laverani*; the Wassermann and Sachs-Georgi reactions were negative.

The course of the disease in the guinea-pig, and the autopsy findings, which have also been accurately described by Mooser (64 *a*) (1924), who experimented with a strain from a wild rat, bear a resemblance to the clinical features of rat-bite fever in man and to the post-mortem findings reported by Kaneko and Okuda (34) (1917).

Various tissues were examined for spirilla using Levaditi's silver-impregnation method, generally with negative result.

Parmanand (79) (1923), Theiler (80) (1926), Worms (72) (1926), and Ruys (81) (1926) were also unable to demonstrate tissue invasion by the spirillum. Parmanand concluded from the examination of stained smears of organs that the spirilla present were all derived from the contained blood. Giemsa-stained smears of the viscera from my experimental guinea-pigs all showed spirilla

usually among red-blood cells, and never in greater number than could be accounted for by the blood present, except in the bone-marrow.

Rabbits. Infection was produced by subcutaneous inoculation at the base of the ear or in the genitals. Two to four days after inoculation there was local swelling and oedema, which attained a maximum in about a week and then subsided; in the fluid expressed from these lesions spirilla were demonstrable—they were, however, never so numerous as in the serum from the primary ulcers in the guinea-pig. Five or six days later a shallow superficial ulcer sometimes formed, which persisted until about three weeks after infection. Enlargement of the regional lymph glands appeared about the eighth day.

There was no definite pyrexia. Spirilla were never demonstrable microscopically in the blood by direct examination, but sub-inoculation into mice showed that blood invasion occurred and lasted for about six weeks.

The general effects in rabbits were varied, first appearing between the 16th and 20th days, and comprising: (1) intermittent conjunctivitis; (2) slight interstitial keratitis (not present in all animals); (3) patchy alopecia about the head; (4) rhinitis with crusting; (5) circinate ulcers on the skin, most constant on the genitals and at the ear bases, but sometimes involving, in addition, almost the whole of the back; (6) generalized lymphadenitis appearing about the end of the seventh week and persisting until after the tenth week.

About three months after infection the active symptoms of the disease disappeared. Spirillicidal antibodies were present in the serum of rabbits after about ten weeks and could be demonstrated by direct *in vitro* tests or by injection of an infected animal. Immune serum in dilutions up to 1 : 16 first immobilized and then lysed the organisms. Normal serum showed no such effect. The spirillicidal action of the immune serum was also exerted against *Spirochaeta laverani* (*v. supra*).

The findings detailed above bear a close resemblance to those of Mooser (64 *b*) (1925) and Worms (72) (1926), and as regards scrotal changes to those of Matsumoto and Adachi (83) (1923). As is stressed by Mooser, by Matsumoto and Adachi, and by Takenaka (84) (1925), who carried out intra-testicular inoculations, the primary changes, and indeed the whole course of the disease, bear a close resemblance to the changes occurring in experimental syphilis of rabbits.

Ruys (81) apparently did not observe an infection in rabbits. This may be due to inoculation with very small doses or to the natural resistance of the rabbits used.

Macacus rhesus. A small male macaque was inoculated subcutaneously in the forearm with infected guinea-pig blood. The temperature rose above normal on the sixth day and remained supernormal until the ninth day; thereafter the pyrexia ran an intermittent course; the febrile periods never lasted longer than a day. The temperature remained normal from the fortieth to the sixtieth day, when observations were discontinued (Chart 3).

On the fifth day after inoculation a swelling developed at the site of inoculation, and on the sixth day the glands in the left axilla were enlarged.

The swelling of the arm persisted for about ten days and then apparently disappeared, but the axillary lymphadenitis was still present. During each febrile attack the left arm swelled, and was apparently sore, and the monkey showed obvious malaise.

When examined 5½ months after infection, the axillary and inguinal glands were found enlarged, but the animal was otherwise healthy. 176 days after infection the glands were dissected out from the left axilla; some were examined histologically and a saline emulsion of the remainder injected into a guinea-pig, which developed the 'latent' spirillosis described above (p. 446). Histologically, the glands showed a marked hyperplasia with a disproportionate increase in the endothelial cells.

Nine months after infection the superficial lymphadenitis was no longer present, and an exploratory laparotomy was performed. The only change observed was enlargement of the mesenteric lymph glands in the ileo-caecal angle. On histological examination these showed marked endothelial proliferation; no inoculations were made.

On the 300th day the abdomen was reopened, and more mesenteric glands were removed and inoculated into a guinea-pig and a mouse. The glands had increased considerably in size in the interval between the two operations, but were not infective.

Frequent microscopic examinations of the blood were made, but no spirilla were detected. They were, however, shown to be present in the peripheral blood by inoculation tests in mice during febrile periods, but never when the temperature was normal.

Cats. Experiments on these animals have been reported by Mooser (64 *c*) (1925) and Kasai (85) (1923). Three cats have been infected experimentally by the writer. The outstanding features of the disease in these animals were: (1) absence of any pronounced local reaction; (2) a relapsing keratitis similar to that in other species; (3) generalized lymphadenitis; (4) the apparent absence of spirilla in the blood on microscopic examination, though infectivity of the blood was demonstrable by inoculation tests in mice.

Ferrets. Experiments were carried out with these animals in view of the reported occurrence of a disease similar to rat-bite fever following the bite of a ferret (*v. supra*). Two animals were infected by subcutaneous inoculation. In both animals there was complete absence of any local inflammatory reaction. In one animal the lymph glands related to the site of inoculation became markedly enlarged. Spirilla were demonstrated in the blood on the 29th, 40th, and 50th days; this animal was killed on the 50th day, and on autopsy the spleen was greatly enlarged. The other animal showed a progressive illness and died on the 77th day with paralysis of its limbs. It had a well-marked bilateral keratitis with profuse discharge. At autopsy local lymph gland enlargement with general lymphadenitis was noted, but only slight involvement of the spleen.

Experiments with Salvarsan.

Mice and guinea-pigs were injected with 'Stabilarsan', the dosage being the same by weight as in man; in every case the spirilla could no longer be found in the blood after 24 hours, but reappeared after 14 days or upwards in mice, and 1 to 2 days in the guinea-pig. In one guinea-pig, which died a few hours after injection, the customary post-mortem increase did not occur, the spirilla diminishing rapidly in numbers until, about 12 hours after death, the blood was microscopically spirillum free.

Discussion.

1. *Identity of spirilla derived from rat-bite fever in man.* Morphologically, the strain described does not differ in any way from those previously reported in other cases of rat-bite fever.

Row (86), on the basis of the small number of nodes and absence of flagella, sought to distinguish the organism he isolated from cases of rat-bite fever (named '*Spirochaete petit*') from those described by Futaki and co-workers. His illustrations of Leishman-stained preparations show no difference between his strain and the shorter forms of the Edinburgh strain, which predominated in the more acute infections in the guinea-pig. The flagella are difficult to stain and the results are variable, hence the apparent absence of flagella is of no significance unless preparations made concurrently with those of a known flagellated strain fail to show flagella; Parmanand, in this way, succeeded in demonstrating flagella. There is, therefore, no reason for differentiating Row's spirochaete from the other strains.

Differences have been described in the infections in guinea-pigs produced by various strains of human origin. The majority of strains have apparently produced an infection identical with the typical experimental disease described above. In some instances the organisms did not appear in the blood until shortly before death; this corresponds to an atypical infection observed in the course of my own experiments. In others, the spirilla never at any stage appeared in the blood, though death occurred. In a fourth group no symptoms, or only very slight symptoms, were produced, and the parasites did not appear in the peripheral blood; this may have been due to the smallness of the inoculum, a latent infection being induced, as in one of the experiments described (*v. supra*): Mooser (64 *b*) (1925) has reported a similar result. It might, however, be explained by assuming that the observations were not continued for a sufficiently long time—in one account they only extended over three weeks. It is noteworthy that in one of the guinea-pigs originally inoculated from the Edinburgh case spirilla did not appear until the 37th day, and at that time the animal seemed in good health.

The above considerations show that pathogenicity to the guinea-pig, depending as it does on amount of inoculum and the individual resistance of the animals, is not a valid criterion for differentiating strains of *Spirillum minus*.

It may be concluded that the human strains so far described are identical.

2. *Identity of strains of human origin with those derived directly from mice and rats.* The presence of spirilla in the peripheral blood of those rodents has been reported by many authors—in the rat by Carter (87) (1887), Lingard (88) (1899), Mezinescu (89) (1909), Carini (90) (1910), Ishiwara and co-workers (91)—11·2 per cent. (1917), Kobayashi and Kodama (92) (1919), Kunhardt (93) (1919), Tejera (94)—10 per cent. (1924), and Aoki and co-workers (95) (1925); in the mouse by Borrel (96) (1905), Breinl and Kinghorn (97) (1906), Wenyon (98) (1906), Löwenthal (99) (1906), Gaylord (100) (1907), Calkins (102) (1907), and Deetjen (103) (1908); morphologically there are no differences between these organisms and the spirillum of *sodoku*—the absence of flagella in descriptions is of no importance on account of the difficulty in staining and the fact that dark-ground illumination was not available when many of them were described.

Only four animal experiments have been described with these spirilla, but the effects of injection are not different from those observed with strains from human cases, e.g. the typical and atypical infections in guinea-pigs. Serologically, only minor differences in degree of immune body formation have been observed.

For comparison, a certain number of experiments in mice, rats, and guinea-pigs were carried out with a strain of *Spirochaeta laverani.* Exactly the same effects were produced as have been described in the case of the strain isolated from the case of rat-bite fever in Edinburgh; also, as already noted, guinea-pig serum exhibited antibody reactions to *Spirochaeta laverani* as well as to *Spirillum minus* and in exactly the same dilution.

Taking these comparative results into consideration along with the occurrence of what I have called atypical infections in guinea-pigs, it seems that there are no reasons for classifying the spirillum of rat-bite fever separately from the organisms described as occurring naturally in rats and mice.

3. *Classification and nomenclature.* Futaki and his co-workers (36 *a*) (1916) named the organism described by them '*Spirochaeta morsus murium*'. Futaki, at the Congress of the Far Eastern Association for Tropical Medicine, held in 1926, still spoke of the *Spirochaete* of rat-bite fever, and Mooser (64 *a, b*) (1924, 1925) classed the organism as a *Treponema.* Manson-Bahr (104) (1925) described it as a *Leptospira*—on what grounds is not apparent.

The absence of an undulating membrane, the rigid body, and multiple flagella distinguish it clearly from the various genera of *Spirochaetes* and indicate that it should be regarded as a spirillum, as suggested by Zuelzer (105) (1921), Robertson (68) (1924), and Ruys (81) (1926).

This being the case, the designation employed by Carter (87) (1887), amended, as suggested by Robertson (68), to *Spirillum minus* in place of *Spirillum minor,* seems justified.

4. *Mode of infection.* (*a*) It has been suggested that the usual mode of infection is by injury to the mouth in the act of biting, causing slight haemorrhage—the blood containing spirilla constituting the inoculum: this theory has been controverted, notably by Mooser (64 *a*) (1924) on the ground that when rats were allowed to bite on wood, iron, or even toast no effusion of blood could be

detected. It must, however, be borne in mind (1) that his animals were tame white rats, which usually have healthy gums, while wild rats frequently suffer from some degree of pyorrhoea—such changes were found in a considerable proportion of wild rats; (2) that biting on a hard substance is not the same as biting into a moderately resistant body, inasmuch as in the former only the edges of the teeth come into contact with the material attacked, while in the latter the gum, especially when unhealthy, can very readily be partly stripped up and slight haemorrhage caused; (3) that in some cases, as recorded by Frugoni (29*b*) (1912) and Borelli (106) (1918), teeth were actually broken off and left in the wound. The violence sufficient to break an incisor tooth is more than sufficient to abrade the unhealthy gum.

Hence, it may be supposed that in the case of an animal with a blood infection, the bite wound may be infected by blood from the injured gums.

(*b*) The spirillum has never been seen in saliva, hence it is frequently stated that infection by contamination of the bite with saliva does not occur. In view of the observation by Mooser (64*a*) (1924) and by myself of desquamated duct-cells and erythrocytes in the duct lumen of salivary glands in our infected guinea-pigs, the possibility of the organism being sometimes present in the saliva is not unlikely.

(*c*) In all those animals whose bite has been commonly described as infectious, viz. rats, cats, and ferrets, and also in guinea-pigs, I have observed an infection of the eye, with profuse discharge, which has been shown definitely in the guinea-pig to be infectious. Mooser (64*c*) (1925) has observed a similar infection in a dog. In the animals which usually convey the disease, viz. rats, 'tertiary' lesions, the material from which contains spirilla, are of almost constant occurrence late in the disease; these have been seen ulcerating and discharging into the bronchi, and may occur in other parts of the body, e. g. ulcerating into the mouth or upper intestinal tract. These tertiary lesions, as they may be called, offer an easy explanation of the entry of spirilla into the bite wound; by secretion from the eyes (or, in the cat at least, from the nose) streaming down the muzzle on to the wound, or into the buccal cavity by way of the nose and naso-palatine duct, or by the passage of material from ulcerated lesions into the mouth.

In only a few cases are observations recorded as to the appearance of the infecting rats. The Japanese, however, are stated by Miyake (1) to believe that infective animals have an emaciated body and a long, pointed snout. In one of the English cases the rat is described as 'mangy', and in the two cases mentioned by Mooser (64*a*) (1924) the rats were described as 'sick'. The emaciation and 'sick' appearance of rats in the tertiary stage of the experimental disease suggest that many of the infectious rats may have been in this stage of the disease, and that accordingly the usual mode of infection is by contamination of the wound with material from the eyes (or nose) or from internal granulomatous lesions.

(*d*) Yamada (60) (1917) and Sano (61) (1917) have recorded cases following the scratch of a cat; Atkinson (107) (1913) described infection from a kitten which had just been playing with a dead rat, and from a ferret which had been

rat-catching. These cases are probably instances of a merely mechanical transfer of infective material on teeth or claws.

5. *Prophylaxis.* In view of the foregoing, it would seem reasonable in cases of rat-bite (or cat- or ferret-bite), if the animal has been caught, to examine the blood for spirilla, as suggested by Clement (108) (1924), and in addition to examine the animal for eye, nose, or visceral lesions, and if such are found, to administer forthwith to the patient a prophylactic dose of salvarsan or one of its derivates.

6. *Bacteriological diagnosis.* In examining a suspected case, serum from the wound, blood, 'juice' aspirated from a lymph gland, and serum expressed from a papule of the rash when present, should be examined by dark-ground illumination and by Giemsa-stained smears. If these results are negative, inoculations of blood drawn during or just after a febrile paroxysm, and of an excised lymph gland, should be made into white mice and guinea-pigs; the inoculations into mice may be intraperitoneal or subcutaneous, but in the guinea-pig it is preferable, in view of the possibility of a latent infection, to inoculate subcutaneously, so that it may be possible, if blood examination of the animal proves negative, to dissect out the regional lymph glands after about three weeks and subinoculate them into another animal; the best site, if the mass of the inoculum does not exclude it, is in the scrotum or labium majus, for here it may be possible to give a positive diagnosis by finding the spirilla in the serum from the local lesion several days before they appear in blood preparations.

If a strain of the organism is available in the laboratory, a direct spirillicidal test or a therapeutic test may be carried out with the patient's serum and normal human serum as a control, as described in the account of the serological experiment in the rabbit.

If syphilis can be excluded, a positive Wassermann reaction would be significant.

Summary.

1. This paper includes a review of the clinical manifestations of rat-bite fever and of past work on the etiology of the disease.

2. A study of the biological characters of the organism and of the experimental disease has been carried out with a strain of the specific organism isolated from a case of rat-bite fever in Scotland.

3. The appropriate designation of the organism is *Spirillum minus* (Carter, 1887), as suggested by Robertson.

4. Reasons have been given for considering the strains of spirillum isolated from cases of rat-bite fever in man and from rodents as identical.

5. Infection probably results from the introduction into the bite of material from late lesions of eyes, nose, lungs, or upper alimentary tract; the possibility of inoculation by blood from the abraded buccal mucosa or by saliva cannot, however, be excluded.

6. The similarity of the experimental disease in certain animals to human syphilis has been demonstrated.

7. Evidence has been adduced to suggest the existence of a strepto- or leptothrix pyaemia transmissible to man by the bite of the rat, which may be confused with true *spirillary* rat-bite fever.

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APPENDIX.

List of chief clinical reports classified according to country, and arranged in chronologica order. * before author's name indicates the demonstration of *Spirillum minus*.

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THE ACTION OF ADRENALIN CHLORIDE ON THE HUMAN HEART[1]

By W. E. HUME

With Plates 15–17

The therapeutic uses of adrenalin chloride would seem to make it necessary that some of its actions on the human heart should be realized. Adrenalin chloride is used very freely for the relief of spasmodic asthma and for other less common conditions. I have heard of many instances of cardiac distress and syncopal attacks following the hypodermic injection of adrenalin chloride for the relief of spasmodic asthma, and the following account probably gives the explanation of these attacks.

The action of adrenalin chloride on the heart and cardio-vascular system of animals has been very fully studied, but there are no records of its direct action on the human heart. Apart from the heart, however, the general effects on the human cardio-vascular system are well known. After an intravenous injection of small quantities of adrenalin chloride the blood-pressure rises considerably, and after initial quickening the heart beats more slowly at the moment when the blood-pressure is highest. As the pressure falls there is again some quickening, but the actual mechanism of the heart throughout its response to an intravenous injection of adrenalin has not been described.

The direct action of adrenalin chloride on the heart has been studied in many animals. For instance, R. H. Kahn (1) published electrocardiograms showing the cardiac effects of intravenous injection of adrenalin in dogs. These electrocardiograms show that in dogs the production of various degrees of heart-block was comparatively frequent, and that ventricular extra-systoles commonly occurred. When adrenalin chloride is added to the perfusing fluid in an isolated rabbit's heart, the rate is considerably accelerated and the strength of the beat enormously augmented.

Pl. 15, Fig. 1 shows the effect of injecting adrenalin chloride into the venous system of a pithed cat. In this experiment no anaesthetic was given after the initial short anaesthetization necessary for pithing. The heart was exposed by removal of the thorax, and levers were attached to the auricles and ventricles. In this experiment the auricles continued to contract forcibly after the ventricles had passed into fibrillation. This was typical of many similar experiments, and

[1] Received November 25, 1927.

it is well known that fibrillation of the ventricles is very apt to occur when adrenalin chloride has been injected into the vascular system of an animal under light chloroform anaesthesia.

During the war I made frequent observations on the effect of injecting intravenously small doses of adrenalin chloride in the human subject. The condition known as D.A.H. or the effort syndrome was, amongst many other speculations, attributed to a supposed hyper-adrenalism. It occurred to me that the subjects of the D.A.H. syndrome would react to injections of adrenalin chloride in a manner somewhat different to normal individuals, if the former were in reality suffering from hyper-adrenalism. For this reason some twenty cases of D.A.H. were injected with either $2\frac{1}{2}$ or 5 minims of a 1 in 1,000 solution of adrenalin chloride, and about 10 controls were similarly investigated. It was not found that there was any material difference either in the subjective sensations or in the results on the heart action and blood-pressure in the two groups. Fig. 2 shows graphically the effects on the ventricular speed and on the blood-pressure. It was always noticed that during the period of highest arterial pressure the heart-rate slowed considerably. The heart-rate was recorded by a continual polygraphic tracing. The subjective sensations were a feeling of faintness and giddiness and a rushing of blood to the head, and there were frequently sensations referred to the chest, such as a feeling of swelling or tightness. Respiration was disturbed, and one or two deep breaths were taken at the moment when the pressure was highest. Tingling and 'pins and needles' were felt in the limbs. These sensations passed off as quickly as the effects on the cardio-vascular system, and both usually lasted from $1\frac{1}{2}$ minutes to 2 minutes. It was occasionally noticed that there was some irregularity of the ventricles during the period of slowing of the heart when the blood-pressure was at its height.

As this work was done in France it was impossible to analyse the detailed action of the heart under the influence of adrenalin chloride, but I was determined on return to England to investigate by means of the electrocardiograph the actual rate and rhythm of the heart. Towards the end of 1919 galvanometric records were taken of individuals after the injection of $2\frac{1}{2}$ minims of adrenalin chloride. Three examples of the effects of adrenalin chloride on the heart will be described. Two of them were very similar, showing the effect usually produced. The third gave a record which seems to indicate that the auricles fibrillated.

Case Reports.

Case I. This subject was a perfectly normal individual of 17 years. $2\frac{1}{2}$ minims of 1 in 1,000 adrenalin chloride together with $2\frac{1}{2}$ minims of distilled water were injected into the right median basilic vein. 5 to 10 seconds after the injection he felt some tingling in the hands and feet and a sensation of giddiness. The heart then seemed to beat more quickly, and he 'felt every beat in all parts of the body'. At this stage there was some blanching, and apparently at the height of the blood-pressure he had a sensation as though his heart would burst.

There was no complaint of headache or pain in the lumbar region, which in other cases was a frequent complaint. Fig. 3 is an electrocardiogram of lead II previous to the injection of adrenalin chloride. Pl. 16, Fig. 4 shows two plates taken as rapidly as possible from lead II, the lower following immediately after the upper. Ventricular complexes of various forms dominate the picture. They appear to arise from ectopic foci in the ventricles, and are grouped very regularly, as shown in Fig. 4, though R 3 of the complete group is somewhat different from the remaining R 3's. In the lower part of the figure the grouping is very similar. Throughout it is difficult to detect with certainty any regular auricular complexes. Fig. 5 was taken immediately after Fig. 4, and the ventricular rate is slower. In the upper record the first three complexes show an auricular rhythm of ectopic origin followed by ectopic ventricular beats, but it is evident that the normal rhythm is trying to reassert itself, and in the lower part of the tracing the heart is beating normally, though rapidly, except for a short break of tachycardia after the third normal response. In Fig. 6 the normal rhythm is re-established except for the occasional appearance of premature auricular or nodal beats.

Case II. This patient was aged 29, and though he was a pensioner for malaria he had not had any recent attacks, and his cardio-vascular system was apparently normal. 2½ minims of adrenalin chloride were injected into the median basilic vein after Fig. 7, showing his normal electrocardiogram, had been taken. He complained of a feeling of tightness in the heart, and palpitation. He blanched, and the breathing was deeper and slower. He had a sensation of stiffness and pain in the small of the back. Pl. 17, Fig. 8 shows that during the time the heart was under the influence of adrenalin chloride there was auriculo-ventricular dissociation. As contrasted with Case I there is definite evidence of auricular contractions throughout the electrocardiogram. In the first part of the electrocardiogram there are abnormal ventricular complexes of ectopic origin, and from both sides of the heart. The second part of the figure shows a similar auriculo-ventricular dissociation, with an attempt to re-establish the normal sequence. Fig. 9 is an electrocardiogram from lead II in which the normal rhythm has been re-established but the speed is excessive.

Case III. A resident medical officer, 30 years of age, volunteered to be the subject of investigation. Except that there were occasional premature ventricular contractions his cardio-vascular system was apparently normal. 2½ minims of adrenalin chloride were injected into the median basilic vein, and after a few seconds he felt a severe constricting pain in the lumbar region as though the muscles were bound together. The lumbar pain worked up to the region between his scapulae, and he felt very short of breath. He was conscious of tingling in the extremities. He became very pale, and his anxiety made it difficult to obtain an electrocardiogram. Fig. 10 was taken previous to the injection. Fig. 11 was taken at the height of the effect, and shows that the auricles are fibrillating, and towards the end of the first record there are two ectopic ventricular beats. Fig. 12 shows the rapid return to normal with an abnormal ventricular complex at the end of the electrocardiogram.

Discussion.

When the observations were being made on individuals suffering from D.A.H. symptoms and on the controls, it was not realized that the effects on the heart were so considerable. Adrenalin chloride is frequently used as a subcutaneous injection in dosage of 5 to 10 minims in various forms of asthma. It is also used in an endeavour to prevent the syncopal attacks of the Stokes-Adams syndrome

in cases of heart-block. Medical men have often stated that they have encountered severe cardiac distress in their patients when adrenalin chloride has been given in these conditions. The alarm has usually been temporary, and I have not heard of any disaster. It would seem very probable that occasionally by the subcutaneous method a considerable quantity immediately reaches the circulating blood, and the cardiac effects are comparable to those described above. When adrenalin chloride is injected into the vascular system of man it would seem to have a direct effect upon the heart-muscle as well as an effect on the myoneural junctions of the sympathetic system. The effect of adrenalin chloride on the heart seems to be in direct proportion to the dilution with which it is injected. 5 minims diluted with 4 or 5 times the amount of distilled water has less direct effect upon the heart than $2\frac{1}{2}$ minims with $2\frac{1}{2}$ minims of distilled water.

Summary.

(1) The general effects of the intravenous injection of $2\frac{1}{2}$ minims of a 1 in 1,000 solution of adrenalin chloride are considered.

(2) Electrocardiographic records are described from individuals into whom a similar injection had been made, and the effects of adrenalin chloride on the mechanism of the heart-beat throughout the experiment have been recorded.

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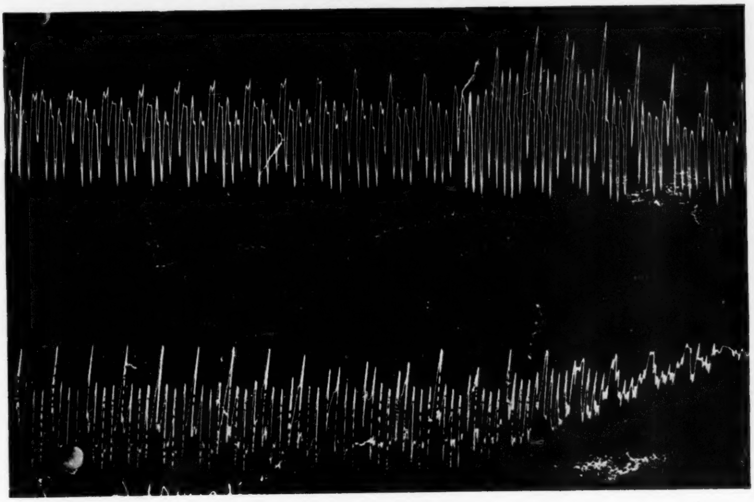

FIG. 1. Intravenous injection of adrenalin into a cat (pithed)
Upper: Auricular contractions. *Lower*: Ventricular contractions

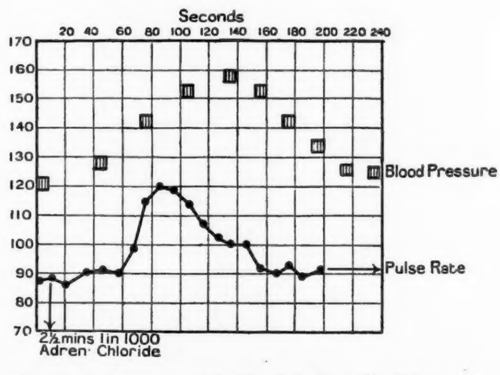

FIG. 2. Intravenous injection of adrenalin into a man
(Blood pressure = systolic pressure)

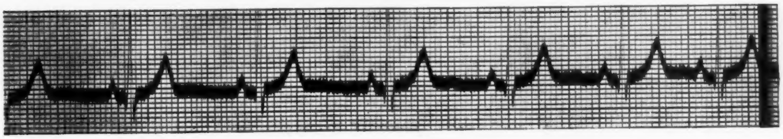

FIG. 3. Normal electrocardiogram from Case I

FIG. 4. Case I. Upper and lower from lead II. Regular repetition of ectopic ventricular beats. Time marker = $\frac{1}{5}$ sec.

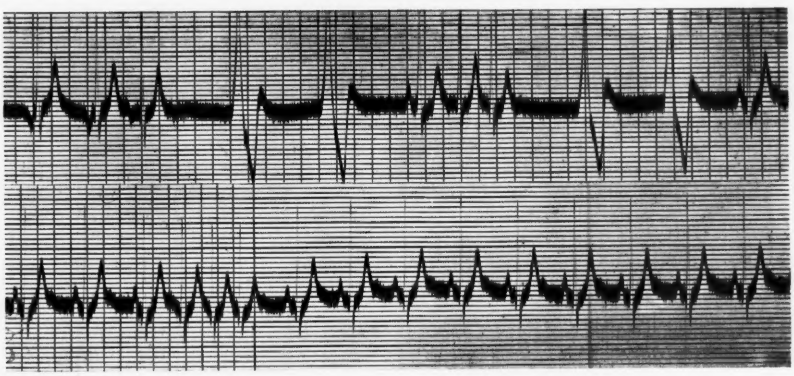

FIG. 5. Case I. Upper and lower from lead II

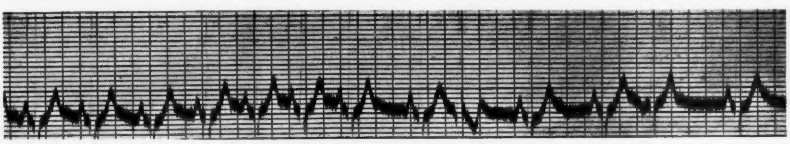

FIG. 6. Case I. Re-establishment of normal rhythm

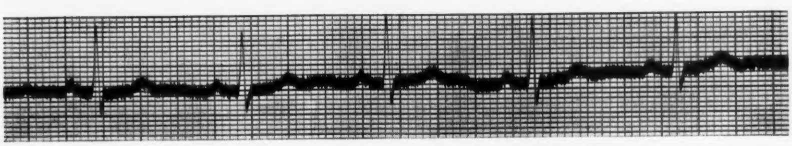

FIG. 7. Normal electrocardiogram from Case II

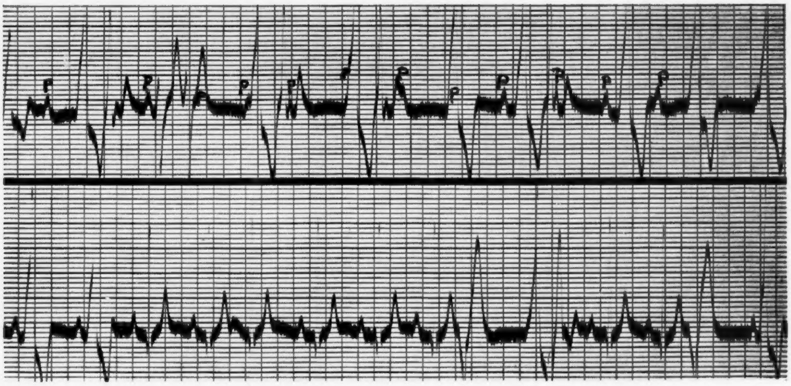

FIG. 8. Case II. Discussion of arhythmia in text

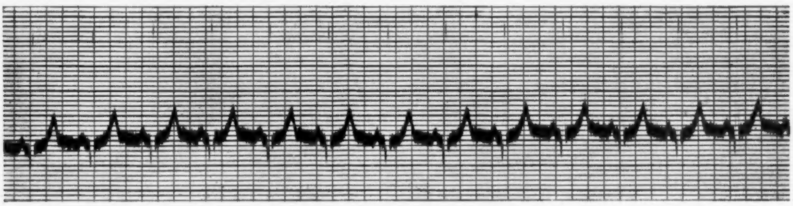

FIG. 9. Case II. Re-establishment of normal rhythm

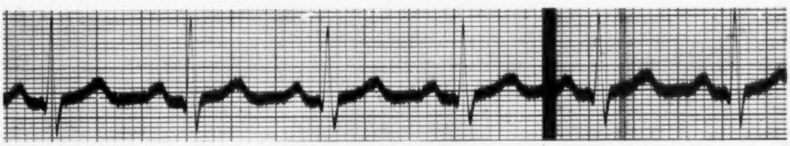

FIG. 10. Case III. Normal rhythm before injection

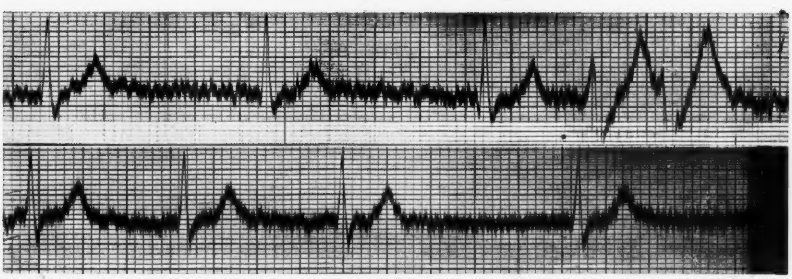

FIG. 11. Case III. Auricular fibrillation. Time marker=$\frac{1}{5}$ and $\frac{1}{25}$ seconds

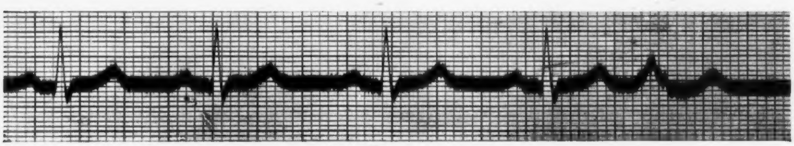

FIG. 12. Case III. Normal rhythm re-established

DIAPHRAGMATIC PARALYSIS AS A THERAPEUTIC MEASURE IN INTRATHORACIC DISEASE[1]

By A. J. CAMPBELL

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I. *Methods of producing Therapeutic Collapse.*

The problem of how to rest the lung is one which has engaged the attention of investigators in recent years, as it has been found that rest, and especially rest associated with compression, favourably influences pulmonary tuberculosis, bronchiectasis, and other intrathoracic conditions; and to do this effectively it has been found necessary to secure a therapeutic collapse, either of a temporary or permanent nature.

At the present time there are several methods employed in collapse therapy:

1. Pneumothorax.
2. Thoracoplasty.
3. Internal and external pneumolysis.
4. Diaphragmatic paralysis.

The last of these, diaphragmatic paralysis, is the most recent method of producing local collapse of the lung; it consists of division or complete evulsion (exaeresis) of the phrenic nerve, resulting in a paralysis of the diaphragm, the dome of which is raised on the affected side, and by this means a collapse of the base of the lung is obtained. This operation has been recently carried out in a series of thirty-one cases at the North Wales Sanatorium. Before proceeding to review these it is proposed to discuss the rationale of the procedure.

II. *The Diaphragm.*

1. *Function of the Diaphragm.*

One of the chief functions of the diaphragm is to keep the lower lobes fully expanded, one-third of the total amount of air inspired being due to its action (Hultkranz (42)). An elevated paralysed diaphragm causes the lung to be forced upwards by the unopposed abdominal muscles, and the base therefore collapses, just as failure of any portion of the chest wall to expand will lead to collapse of the underlying lung.

[1] Received June 27, 1927.

2. *Relation to Pulmonary Diseases.*

(a) *Position.* Several observers have noted that a low portion of the diaphragm is frequently associated with pulmonary tuberculosis; it is probably due to a general loss of muscular tonicity more or less characteristic of all asthenic states (Wenckebach (95)); the diaphragm in its descent pulls down with it the heart and aorta, causing these structures to become more or less elongated—a condition often seen in the radiograms of tuberculous patients. Argentina (5) is of a similar opinion, and explains the feeling of well-being experienced by a phthisical woman during pregnancy to the fact that the diaphragm is pushed upwards by the gravid uterus.

(b) *Movements.* Phrenic paresis, manifested by diminution and lagging of the movement of the diaphragm, is found in a considerable proportion of cases of early tubercle (Williams's sign (96)); it is possibly due to an apical pleurisy causing pressure on the nerve (De la Camp and Mohr (19)), and may cause shoulder pain referred to the area of cutaneous distribution of C 3 and 4, and even persistent singultus. Restriction of movement of the diaphragm may be due to other causes, such as diaphragmatic pleurisy, with or without adhesions, or simply to a muscular spasm endeavouring to protect a diseased focus in its neighbourhood.

III. *Effects of Diaphragmatic Paralysis.*

1. *On the Muscle.*

(a) *Position.* When the diaphragm is paralysed the dome rises on the side which is affected, higher on the right side, because it is pushed upwards by the liver, aided by the intra-abdominal pressure, while on the left side the heart lies to a certain extent in apposition with the diaphragm, and so more or less impedes its progress as it encroaches on the intrathoracic space. The height attained is generally 4–8 cm. on the right, 2–6 cm. on the left. It usually happens that, unless hindered by pleural adhesions or a stiff fibrotic lung, the diaphragm continues to rise into the chest some months after the paralysis has been produced. The clinical signs it gives rise to are: indrawing of the epigastrium with a certain loss of resistance of the abdominal muscles (Gerhardt (30)), the affected half of the thorax makes greater excursions, the ribs run less obliquely, the intercostal spaces are broader, and the breast stands higher on the side which is affected. Litten's sign is absent.

(b) *Movements.* When its nerve supply has been interrupted the affected half of the diaphragm, having risen to the full expiratory position, may have slight normal movements imparted to it by the pull of the central tendon, but as a rule any movement which occurs is opposite to the normal, i. e. paradoxical, movement (Kienbock's phenomenon (49)) due to the respiratory variation in the intrathoracic pressure. This is not observed in every case, however, but is generally seen unless the diaphragm is fixed by adhesions or a basal effusion is

present. In cases where one is doubtful as to the presence of paradoxical movements Bittorf's (10) test is of value. When under the X-ray screen the patient is asked to hold his nose and mouth tightly closed and try to take a deep inspiration, the paralysed side of the diaphragm rises while the unparalysed side descends. If examined carefully most cases will show this phenomenon, which is one of the most valuable signs affording evidence of a total phrenic lesion.

Sometimes in the presence of adhesions in the pericardio-phrenic space the paralysed diaphragm may be seen to have transmitted cardiac pulsations.

(c) *Muscle Tone.* Some observers (Ken Kure (44) and others) have stated that the muscle tone of the diaphragm is maintained after section of the phrenic nerve by those fibres which reach the diaphragm via the sympathetic. Felix (20), on the other hand, has produced experimental evidence to show that this is not muscle tone at all, but simply a mechanical tension due to the forces acting on the paralysed structure (these forces being the elastic pull of the lung, the pressure of the abdominal viscera, and the pull exerted by the other half of the diaphragm).

(d) *Atrophic Changes.* When paralysed the diaphragm atrophies and eventually becomes a parchment-like membrane, and this degeneration is entirely unilateral, as Schlaepfer (82, 83) has observed in experiments on dogs.

2. *Effect on Thoracic Capacity. Spirometry.*

On the right side the capacity of the chest is diminished by 400–800 c.c., i. e. one-sixth to one-third of its volume (total capacity 2,400 c.c.). Goetze (31) stated that a successful phrenicotomy is as good as a pneumothorax, and this may possibly be true in those cases where a very high rise takes place.

3. *Effect on Respiration.*

A diminution of volume to this extent (i. e. one-sixth to one-third) does not give rise to dyspnoea, as a much greater deficiency of respiratory function occurs in pneumonia and other diseases of the lung without causing any shortness of breath. In fact, Jehn (43), Sauerbruch (77), and others have performed bilateral phrenicotomy in certain cases and have seen no noteworthy disturbance. One such case (quoted by Jehn) led an active life for 3½ years after bilateral phrenicotomy and was never dyspnoeic.

4. *Effects on Intrathoracic Structures.*

(a) *The Lung.* Along with this lessening of thoracic capacity there is naturally a decrease in the volume of the lung, especially if there are adhesions in the costophrenic space. The lessening of volume and the relaxation of the base of the lung, due to the elimination of the pumping action of the diaphragm, are factors which cause a certain amount of pulmonary rest, which not only affects the base, but the apex also, in cases where the intrapleural space is free from adhesions, and this is supported by the fact that many apical lesions have materially improved after the diaphragm has been paralysed (Goetze (35)).

(b) *The Heart.* In a left-sided phrenicotomy the rising dome of the diaphragm may displace the heart upwards, and in this way it may possibly relieve palpitations and tachycardia from the drag of pleural adhesions; a paralysis of the left dome of the diaphragm relieved these symptoms in a case in our series with extreme cardiac displacement.

(c) *The Oesophagus.* It has been observed in animals that after the diaphragm has been paralysed there is some difficulty in the filling up of the oesophagus from the cardiac end of the stomach, and consequently a tendency to prevent the act of vomiting (Klee (50)). This may possibly explain why phrenicotomy causes a relief of the vomiting produced by basal adhesions in a left-sided pneumothorax.

5. *Effect on Labour.*

Paralysis of the diaphragm does not cause any interference with the course of labour; (Lange (56)) reports a case in which phrenicotomy was done upon a patient six months pregnant and labour occurred normally.

6. *Effects in Elderly Individuals.*

In elderly people, in whom diaphragmatic breathing more or less predominates, phrenicotomy does not lead to respiratory embarrassment. Lange (56) believes that in bilateral diaphragmatic paralysis with ossification of the costal cartilages the patient will suffer from increased dyspnoea, but so long as the thorax is movable no danger need be expected in a unilateral case.

IV. *Therapeutic Diaphragmatic Paralysis. History.*

Diaphragmatic paralysis was first suggested as a therapeutic measure in disease of the lung in 1911 by Steurtz (88), who divided the phrenic nerve in the neck in cases where the lower lobe contained a tuberculous or bronchiectatic cavity, and when artificial pneumothorax treatment was impossible on account of pleural adhesions. Sauerbruch (78) in 1913 at the Munich clinic reported five cases in which phrenicotomy had been performed with marked benefit; at the time he first used it he was unaware of Steurtz's earlier proposal. In two cases of bronchiectasis the sputum was reduced by one-half; in one case of pulmonary tuberculosis with bilateral signs the cough ceased; in two cases with physical signs confined to the upper lobe phrenicotomy stopped the cough and expectoration. Oehlecker (70) (1913) found it of value in causing a diminution of a basal sinus in tuberculous empyema, and also in relieving shoulder pain, when this is of phrenic origin. Carl (15) (1914) made some interesting observations from animal experiments. In rabbits with a unilateral diaphragmatic paralysis he injected two milligrams of tubercle bacilli intravenously, and noticed that the disease failed to develop on the paralysed side. Goetze (31) (1920) suggested the use of temporary diaphragmatic paralysis; the methods he used will be discussed later.

In Great Britain, Morriston Davies (63) has done phrenicotomy since 1914, and has found it beneficial in conjunction with artificial pheumothorax, also independently. He emphasizes its value in affording relief from distressing symptoms—e. g. irritating cough, pain from basal adhesions, &c.

Felix (20) (1922) published the results of his investigations regarding the nerve supply of the diaphragm, and in view of their important bearing on therapeutic diaphragmatic paralysis it is necessary to give this question fuller consideration. The following account of the anatomy of the phrenic nerve is taken chiefly from the elaborate description given by Felix.

V. *Nerve Supply of the Diaphragm.*

1. *Motor Nerves.* The diaphragm receives its main nerve supply from the phrenic nerve, which supplies fibres for practically the whole of the muscle except a small area posteriorly taking origin from the twelfth rib, which is supplied by the twelfth intercostal. There is another small area lying in front of the vertebral column, which is supplied by phrenic and sympathetic fibres conjointly.

2. *Sensory Nerves.* The central portions of the pleural and peritoneal surfaces of the diaphragm receive their sensory nerve supply from the phrenic, while the outer edges are supplied by the last six [intercostals. Thus it is that a disease process occurring in the neighbourhood of the diaphragm may cause pain referred to the area of the cutaneous distribution of C 3 and 4 (N. supraclavicular), or to the areas supplied by the last six intercostals (lower part of the thorax and hypochondrium), depending upon whether the stimulus arises in the central or peripheral parts of the muscle.

3. *Course of the Phrenic Nerve.* The phrenic nerve arises chiefly from C 4, but it also receives fibres from C 3 and 5. Its main trunk runs inferiorly and medially from the lateral border of the scalenus anticus, crossing that muscle obliquely from above, downwards and inwards. It runs below the sternomastoid, and is crossed by the omohyoid and by the transverse scapular and transverse cervical vessels. It then passes in front of the subclavian artery, between it and the subclavian vein, and, as it enters the thorax, crosses the internal mammary artery near its origin. Within the thorax it descends vertically in front of the root of the lung, and then between the pericardium and mediastinal pleura to the diaphragm, where it divides into branches which pierce that muscle and are distributed to its under-surface ; in the thorax it is accompanied by the pericardiophrenic branch of the internal mammary artery.

4. *Relation of Sympathetic and Phrenic.* According to Felix (20) there is a strand of sympathetic nerve fibres running within the nerve sheath of the phrenic, and these fibres are connected with a plexus overlying the dome of the pleura, which is known as the suprapleural plexus. Local pain produced by disease at the apex of the lung may be due to pressure on this plexus, which may

also cause a phrenic paresis manifested by diminution of the movements of the dome of the diaphragm on the affected side (Williams's sign (96)). These sympathetic fibres unite with the motor fibres of the phrenic on the peritoneal surface of the diaphragm.

5. *The Accessory Phrenic.* Apart from the sympathetic, other motor nerve fibres may join with the phrenic nerve before it reaches the diaphragm, and it is to these that the term accessory phrenic is given. An accessory phrenic is present in about 25 to 30 per cent. of normal individuals, and is not usually divided by a phrenicotomy at the level of the omohyoid muscle, and hence diaphragmatic movements persisting after this operation are generally due to its presence. It arises from C 5, and frequently runs in contact with the nerve to the subclavius, leaving it just before it pierces the subclavius muscle; but it may consist of fibres from the hypoglossal, spinal accessory, vagus, or the suprascapular nerves, either directly or through the ansa hypoglossi. The accessory phrenic generally unites with the main phrenic nerve after crossing the subclavian artery just under the sterno-clavicular joint, or may unite higher than this, near the usual site of phrenicotomy above the omohyoid, or lower, close to the hilus of the lung.

Felix (20) therefore advised exaeresis of the phrenic nerve—i.e. complete evulsion of the whole nerve together with the terminal filaments from the diaphragm. This operation not only resects the main trunk, but also interrupts all its connexions with the accessory phrenic and the sympathetic from the neck, suprapleural plexus, and the upper part of the thorax.

6. *Nerve Regeneration.* Diaphragmatic movement following phrenicotomy is by no means always due to the presence of an accessory phrenic, for it occasionally happens that the phrenic nerve regenerates after division. The shock of the operation of division or resection is frequently sufficient to inhibit the action of the accessory phrenic when this is not divided, but this inhibition seldom lasts longer than a few weeks; when the return of function is due to regeneration, it does not occur until three to four months have elapsed.

VI. *Methods of producing Diaphragmatic Paralysis.*

A. *Temporary Methods.*

It has been suggested that some method might be devised whereby the phrenic nerve could be put out of action sufficiently long to permit of healing a tuberculous lesion without permanently interfering with the function of the diaphragm. Several measures have been carried out with this end in view, but unfortunately they have, so far, met with comparatively little success.

1. *Contusion of the Nerve.* Friedrich (25) recommended bruising the nerve with forceps so as to rupture the nerve fibres, while at the same time maintaining the continuity of the nerve sheath, and thus allow of the possibility of regeneration. In the majority of his cases, however, he did not succeed in obtaining a satisfactory paralysis.

2. *Freezing the Nerve.* Fischer (23) advised freezing the nerve for 2–3 m.m. only by spraying with ethyl chloride for fifteen minutes. Goetze (33) has combined this with resection of the nerve to the subclavius to get rid of the accessory phrenic; the paralysis obtained lasted three to four months, and Goetze recommends that this procedure (which he calls temporary radical phrenicotomy) should be used in certain selected cases, e. g. in severe cases of pulmonary tuberculosis with a certain degree of involvement of the relatively sound lung, in cases of persistent singultus, and in chronic pleural empyema.

3. *Intraneural Injection.* Intraneural injection with 70 per cent. alcohol has been recommended by Goetze; while Henschen (39) has obtained a paralysis by blocking the nerve with novocain. In these cases regeneration occurs in about three months.

4. *Section and Suture.* Section and immediate suture of the nerve has been performed. Regeneration may be expected in four months (Kroh (52).)

B. *Permanent Methods.*

1. *Simple Phrenicotomy.* Simple division of the phrenic nerve in the neck was the operation originally recommended by Steurtz (88) in 1911. It has the disadvantage that it fails to produce diaphragmatic paralysis in 25 to 30 per cent. of cases owing to the existence of an accessory phrenic, as happened in one of our series. However, as we have seen, a certain number of cases have occurred where the phrenic nerve has regenerated following phrenicotomy.

2. *Radical Phrenicotomy.* Radical phrenicotomy implies resection of the accessory phrenic as well as the main stem. The operation performed by Goetze (35) consists of simple phrenicotomy at the level of the omohyoid, and resection of the nerve to the subclavius, in which the fibres of the accessory phrenic generally run. It is a somewhat difficult operation, and deals with only one, although, nevertheless, the most common, variety of accessory phrenic.

3. *Phrenic Exaeresis (or Evulsion).* This is the operation recommended by Felix (20) and practised extensively at the Munich clinic, and it was also the operation done in the majority of our cases. The accessory phrenic, as we have already seen, generally joins the main nerve just under the sterno-clavicular joint, and if lower than this is practically always above the hilum of the lung. The distance of the hilum of the lung from the usual site of the phrenicotomy is 12 cm.; speaking generally, it is within this distance that the fibres of the accessory phrenic enter the main stem. Accordingly, by evulsing the first 12 cm. of the phrenic nerve and so including all the varieties of accessory phrenic, one ought to be successful in securing a satisfactory paralysis of the diaphragm.

VII. *Indications for Phrenic Exaeresis.*

1. *Basal Infections.*

(*a*) Bronchiectasis, (*b*) fibrosis of the lung, (*c*) chronic pleural empyema, (*d*) abscess of the lung and hydatid disease, (*e*) pulmonary tuberculosis.

2. *Special Indications in Pulmonary Tuberculosis* (apart from basal lesions).
   1. When pneumothorax has failed.
   2. In bilateral cases with extensive disease.
   3. In early unilateral cases not responding to sanatorium treatment.
   4. As a measure for symptomatic relief in (*a*) cough, (*b*) copious expectoration, (*c*) pyrexia, (*d*) haemoptysis, (*e*) pleural pain, (*f*) vomiting, (*g*) dyspnoea, (*h*) hiccup, (*i*) palpitations and tachycardia from embarrassment of the heart.
3. *Combined with Pneumothorax.*
   1. When there are basal adhesions.
   2. To assist re-expansion of the lung.
   3. In all cases it lengthens the intervals between refills, and tends to prevent effusion and mediastinal displacement.
4. *Combined with Thoracoplasty.*
   1. As a test of the opposite lung.
   2. To assist by collapsing the base.
   3. To prevent aspiration to the lower lobes.

1. *Basal Infections.*

(a) *Bronchiectasis.* The chief indication for phrenic exaeresis is in basal infections. In the treatment of bronchiectasis it often gives most dramatic results; speaking generally the results of treatment appear to be more promising in bronchiectasis than in tubercle, and this is possibly owing to the fact that post-pneumonic bronchiectasis involves the lower lobes rather than the upper; whereas in tubercle the reverse is more often the case, the lesion in the lower lobe being generally secondary to apical involvement; moreover, in bronchiectasis the lesion is more frequently limited to one lobe. The rapid decrease in the copious foul expectoration is often quite remarkable, as the following case will show:

Case I. G. D., female, aged 17. As a child never robust, cough and sputum from the age of 10 till 14. Remained well for three years, then developed double pneumonia (January, 1926); three weeks later had a sudden attack of pain in the right side diagnosed as pleurisy. Remained in bed, more or less febrile, until admission on March 12, 1926. Then chief symptoms, cough and expectoration, copious, easily coughed up, and offensive; amount 8 oz. per day; repeated examinations negative for tubercle. Physical examination showed dullness, increased V. R. and V. F. at right base, with evidence of consolidation R. U. L. X-ray: striation at the right base, especially towards the diaphragm, and diffuse opacity over the left upper lobe. Phrenic evulsion performed April 19, 1926; the right phrenic completely evulsed together with the terminal filaments; total length $43\frac{1}{2}$ cm. Following operation quantity of sputum gradually diminished; temperature became normal. The right dome of the

diaphragm raised 7 cm. with paradoxical movements; opacity in the right lung less marked. Patient continued to improve, went through the usual course of graduated labour, and discharged on September 3, 1926, free from symptoms and afebrile; all the moist sounds at the right base had disappeared.

(b) *Fibrosis of the Lung.* Phrenic evulsion is of value not only in the treatment of bronchiectasis, but it has also been employed prophylactically in those cases of post-pneumonic fibrosis which, if left untreated, often go on to bronchiectatic changes. The fibrotic process normally causes a pulling in of the chest wall, diaphragm, and mediastinum, and there is a certain amount of resistance to this, shown by the attempt on the part of the tissues to return to their normal position, the result being an arrest of the process of contraction; the walls of the bronchi are pulled upon, and become dilated. This tendency is prevented in the lower lobes by the relaxation of the lung produced by the rising dome of the diaphragm.

(c) *Chronic Pleural Empyema.* Several continental observers (Goetze (35), Brunner (13), &c.) have stated that in chronic pleural empyema with a sinus over the lower lobe, diaphragmatic paralysis assists by diminishing the size of the sinus and promotes healing; in such cases it will materially assist a subsequent thoracoplasty, if this is considered necessary.

(d) *Abscess of the Lung and Hydatid Disease.* In all pathological conditions associated with a cavity in the lower lobe it has a distinct value. Good results have been recorded in cases of abscess of the lung and in hydatid disease; once the cyst has been removed it materially assists by helping to bring the walls of the cavity in opposition, as the following case shows:

Case II. A. A., male, aged 20. In February, 1926, pain in right side, treated as pleurisy; a fortnight later began to have sputum, on one or two occasions streaked with blood. Seen by Tuberculosis Officer and no evidence of tuberculosis found, but admitted to hospital for observation. In July transferred to the Sanatorium; on admission symptoms were pain in the right side, slight cough, and about half an ounce of sputum daily. Sputum negative for tubercle bacillus and no evidence of hydatid hooklets; had always kept dogs at home and had been more or less in contact with them all his life. Physical examination showed relative dullness just below and external to the right nipple anteriorly and posteriorly; a similar area in the scapular line from the fifth to the eighth rib with a few crepitations. X-ray: an opaque circumscribed elliptical shadow in the area corresponding to this, surrounded by apparently normal lung. Hydatid disease diagnosed, and it was decided to remove the cyst by operation, which was done in two stages. Cyst examined, found to be a hydatid with secondary pneumococcal infection.

Cough and expectoration still persisted following the operation (though much less than formerly), and it was decided to paralyse the right dome of the diaphragm with a view to bringing the walls of the cavity into closer apposition. The phrenic nerve was found crossing the scalenus anticus. Pulling upon the nerve caused considerable pain, radiating down the back and the right arm. Evulsion therefore not attempted, 4 cm. being resected. Following the operation, cough and expectoration ceased, and the patient was discharged from the Sanatorium fit for work. In this case phrenic evulsion was responsible for a certain amount of the improvement, assisting by the production of basal collapse and approximating the walls of cavity after the cyst had been removed.

(e) *Pulmonary Tuberculosis.* (1) *As an independent therapeutic measure.* In all tuberculous infections of the lower lobe, diaphragmatic paralysis is advantageous, and in favourable cases it may effect a cure, especially if the upper lobe is not markedly affected. The following case, where the signs were chiefly basal, is one which was improved after phrenic evulsion:

Case III. G. B., female, aged 31. Married. Patient's illness began with an attack of influenza in December, 1924; cough, expectoration, and a feeling of general weakness and lassitude followed. Tubercle bacilli found in sputum. Admitted in February, 1925. Physical examination showed some harsh broncho-vesicular breathing at the right apex, with crepitations towards the base posteriorly. X-ray: diaphragmatic movement was poor on either side, and the heart displaced to the right; a broad band of opacity extending just above the right dome of the diaphragm; lesion of the lower lobe diagnosed and phrenic exaeresis advised. In May, 1925, 10 cm. of the right phrenic nerve were evulsed. The nerve lay on the lateral side of the scalenus muscle, which it crossed just above its insertion into the first rib. With it ran another nerve, the two being closely connected in the upper part of their course. The second nerve left the phrenic in the lower part of the neck and turned outwards across the posterior triangle. After operation right dome of the diaphragm immobile and raised, with acute peaking 4 cm. above the left; no paradoxical movements. A month after the operation, cough almost disappeared and no expectoration, just a little more dyspnoea than before, but patient felt much improved generally. Discharged in September, 1925, free from all symptoms. Improvement was maintained. Disease can now be regarded as quiescent (July, 1927).

2. *Special Indications in Pulmonary Tuberculosis.*

Apart from purely basal cases there are other circumstances in which phrenic exaeresis is advantageous in pulmonary tuberculosis:

1. When pneumothorax has been unsuccessful on account of adhesions an improvement can sometimes be brought about by diaphragmatic paralysis. It sometimes happens that in these cases not only are the two layers of the pleura in contact, but the phrenic nerve itself is embedded in fibrous tissue, rendering extraction difficult and frequently only partial. In progressive febrile cases of the caseous or exudative type, where pneumothorax has failed, Goetze (35), Frisch (28), and Brunner (13) report favourable results.

2. In bilateral cases with extensive disease diaphragmatic paralysis effects a certain degree of improvement with diminution of cough and sputum. It presents this advantage over other methods employed in collapse therapy, that bilateral disease is not a contra-indication.

3. For cases of early unilateral tuberculosis which do not show reasonable promise of becoming arrested by continuation of sanatorium treatment, J. Alexander (2) recommends it to replace pneumothorax. It possesses advantages over the latter in that complications occur less frequently, and that the operation is concluded at one sitting. Advantages of performing phrenic exaeresis in the earlier rather than in the late stage of tuberculosis are:

(*a*) The diaphragm is less apt to be bound down by adhesions, which would keep it from attaining its highest possible level if paralysed.

(*b*) There is less possibility of the presence of superficial caseous lesions, to which the phrenic nerve might be adherent, and which it might tear open when it is extracted from the upper part of the thorax by the operation of exaeresis.

4. In some cases phrenic evulsion is employed not primarily with a view to arrest of the disease, but simply for the relief of symptoms. (*a*) *Cough.* Morriston Davies (66) states that he has found phrenic evulsion valuable in the relief of cough, especially that dry irritating cough which is set up when the base of the lung is adherent to the diaphragm. Speaking generally, the act of coughing is easier after the diaphragm has been paralysed, as when relaxed it exercises less resistance to the intra-abdominal pressure than normally. Thus expectoration is easier and there is less tendency for the secretions to accumulate (Lange (56)). (*b*) *Copious expectoration.* Phrenic evulsion often results in a decrease in the amount of sputum, which in many cases is quite remarkable. (*c*) *Pyrexia.* A fall of temperature can only be expected where the rest and the local collapse produced have been sufficient to affect the lymphatic circulation and cause a diminution in the absorption of toxic material. Goetze (34) and Brunner (13) have demonstrated this in caseous lesions of the lower lobe with cavity formation. (*d*) *Haemoptysis.* It helps to control haemoptysis in cases where pneumothorax is impossible owing to adhesions; it is more likely to succeed if the bleeding comes from the lower lobe. Morelli (61) and Přibam (74) have found it of value in these cases. (*e*) *Pleural pain.* Continuously recurring pain, which is due to the contact of inflamed surfaces of the diaphragmatic and the visceral pleura at the base of the lung, often yields to this form of treatment when simpler measures have failed. (*f*) *Vomiting* associated with coughing is often relieved by it. It is particularly valuable in the vomiting associated with basal adhesions in pneumothorax, as will be seen later. (*g*) *Dyspnoea.* Contrary to expectation, dyspnoea is often relieved rather than increased after phrenic evulsion. This is probably owing to the fact that the rising diaphragm approximates the parietal and visceral layers of the pleura in a case where these surfaces have been separated by a retracted lung; in such a case the pulling of adhesions may cause a tonic spasm of the diaphragm—an additional factor in the production of dyspnoea (66). (*h*) *Hiccup.* Sauerbruch (77) has found it valuable for the relief of this symptom, which is often due to the pressure of thickened pleura on the nerve at some part of its course. (*i*) *Palpitations and tachycardia.* When these symptoms are due to the mechanical cause, such as the drag of adhesions or fibrosis of the lung, the relaxation of the paralysed diaphragm is often sufficient to give relief.

3. *Phrenic Evulsion combined with Pneumothorax.*

1. When basal adhesions are present. The presence within a pneumothorax cavity of adhesions which are attached to the diaphragm is one of the conditions which most frequently demand phrenic exaeresis. Such adhesions may give rise to pain, dyspnoea, and irritating cough, and cannot usually be divided by cauteriza-

tion. One generally finds that after phrenic exaeresis the intrapleural pressure can be increased without the risk of causing tearing, and that the distressing symptoms the adhesions produce are almost entirely relieved, as in the following case:

Case IV. V. T., female, aged 24. Lassitude since July, 1922, then a dry cough, and in December, 1922, pleurisy of the right side: no effusion. Sanatorium treatment advised in February, 1923. On admission complained of a slight cough; no sputum, but lassitude and dyspnoea on slight exertion, afebrile. Physical examination showed signs of disease (left upper lobe). Several months of sanatorium treatment produced little change; pneumothorax commenced in July, 1923. A satisfactory collapse obtained accompanied by clinical improvement: X-ray showed two divergent adhesions passing from the base of the lung to the anterior part of the diaphragm. The patient complained of vomiting immediately after and just before a refill, due presumably to the adhesions; thoracoscopy showed a band firmly adherent to the pericardium. Cauterization of the adhesion (i. e. internal pneumolysis) was therefore impracticable. Meanwhile the lung was gradually re-expanding, necessitating more frequent refills, with as a result more marked gastric symptoms; phrenic exaeresis advised with a view to relieving the condition. Operation performed December, 1924, 9 cm. of the left phrenic nerve being evulsed. Left dome of the diaphragm paralysed and raised about 1·5 cm. above the right. Pneumothorax treatment discontinued and lung allowed to re-expand. The gastric attacks continued, though less severe, and finally ceased as the diaphragm gradually rose. The Tuberculosis Officer reports she is still free of symptoms (August, 1927).

This case illustrates the fact that diaphragmatic adhesions may produce untoward results in a case of pneumothorax, even when a good collapse of the lung has been obtained with apparent arrest of the disease. The only symptoms which persisted after pneumothorax treatment were dyspnoea and periodic attacks of vomiting; the dyspnoea was entirely relieved and the gastric attacks were less severe and less frequent after the diaphragm had been paralysed.

2. When the lung is allowed to expand. When the period of artificial pneumothorax treatment has come to an end and a re-expansion of the lung is desired, this re-expansion takes place much more gradually when the diaphragm has been paralysed. 'To release an artificial pneumothorax'—to quote the words of John Alexander (3)—'and permit a scarred, shrunken lung to re-expand in an attempt to meet the chest wall is a hazardous procedure, not rarely followed by emphysema, mediastinal displacement, dyspnoea, effusion, pain, unfolding of cavities, lighting up of incompletely encapsuled foci, and reactivation of the tuberculous disease. The narrowing of the chest, caused by the mounting of the diaphragm, largely compensates for the disproportion in volume between the unchanged capacity of the hemothorax and the diminished volume of the shrunken fibrotic lung.'

3. Before every pneumothorax. Several authorities (Goetze, Zadek (98), J. Alexander (3), &c.) go so far as to recommend that every pneumothorax should be preceded by phrenicotomy or phrenic evulsion, the operation being carried out eight to fourteen days before inducing pneumothorax. Advantages which they claim are:

1. More complete rest of the lung.
2. Mediastinal displacements are much less frequent.
3. Effusions occur less frequently, and when they do occur they are less in amount.
4. The diminution in the intrapleural space means that there is less gas used, and the more complete rest means that absorption takes place much more slowly; the interval between the refills is lengthened from one-quarter to one-third (Zadek (98)).

There are, however, certain disadvantages in performing this operation in every case of artificial pneumothorax:

1. Cases occur in which, after giving up pneumothorax on one side, it is necessary later, on account of further extension of the disease, to do it on the opposite side also, and if the respiratory activity of the lung which is being allowed to expand has been permanently diminished by diaphragmatic paralysis, pneumothorax cannot be carried out in the other lung.

2. In cases where pneumothorax has been already started, and there is a high positive pressure, diaphragmatic paralysis is of little use, as the diaphragm is already compressed from above by the intrathoracic pressure, and therefore cannot rise satisfactorily.

3. A similar state of affairs exists in cases of pneumothorax complicated by effusion, as the weight of the exudate prevents the diaphragm rising satisfactorily.

4. *Phrenic Exaeresis as a Preliminary to Thoracoplasty.*

Phrenic exaeresis performed in association with thoracoplasty serves three purposes:

1. As a test of the opposite lung.
2. To assist by collapsing the base of the lung.
3. To prevent the spread of infection to the lower lobes.

1. *As a test of the opposite lung.* Sauerbruch (77) has used it as a test of the opposite lung in cases where thoracoplasty is being considered. If, after a functional rest of the worse side, the physical signs of disease on the other side are increased, it means that the lung will not stand a further collapse, and thoracoplasty is therefore contra-indicated. If improvement follows after phrenicotomy then the more extensive operation may be safely carried out.

2. *To assist by collapsing the base of the lung.* Most authorities (Brunner (13), J. Alexander (3), Morriston Davies (66), &c.) are now agreed that paralysis of the diaphragm should precede every thoracoplasty in order to obtain the maximum degree of collapse. It is of value in improving the patient's general condition before the major operation, and it is generally found that a much less extensive resection of ribs is required after the diaphragm has been paralysed.

3. It prevents the spread of infection to the lower lobes, and any catarrhal process already there tends to subside in a much shorter time.

5. *Contra-indications for Phrenic Exaeresis.*

1. Bilateral fibrosis with pleural involvement on account of the rigidity of the thorax.

2. With severe emphysema of the opposite side, as any lessening of the respiratory activity will give rise to dyspnoea.

3. Several authorities (Sauerbruch (77), Brauer (11), Spengler (87), &c.) are convinced that in acute caseous tuberculosis diaphragmatic paralysis is of little value as an independent measure apart from pneumothorax and thoracoplasty, and regard this form of the disease as a contra-indication to its employment, except as a supplementary operation. Others (Goetze (34), Frisch (27), Brunner (13)) report good results in cases of this type.

VIII. *Operation.*

The operation is performed under local anaesthesia; half an hour before anaesthetization is begun, the patient is given $\frac{1}{3}$ gr. of omnopon subcutaneously. The local anaesthetic used is novocain 0·75 per cent. with adrenalin 1 in 1,000—12 minims to 1 oz.; it is injected an hour and a quarter before commencing. Local anaesthesia may have the disadvantage of increasing the difficulty by producing oedema of the tissues and altering the anatomical relations, but if the anaesthetization is done well and sufficiently long beforehand, there should be no oedema. It has the advantage that with its use one can rely on the sensations of the patient to assist in identifying the nerve.

The patient's head is turned towards the opposite side so as to stretch the sternomastoid and expose the posterior triangle. An incision two and a half inches long is made from the middle of the posterior border of the sternomastoid, running obliquely downwards to about the middle of the clavicle. After dividing the platysma, superficial cervical fascia, and adipose tissue of the posterior triangle, on opening the anterior layer of the deep cervical fascia, the nerve is exposed as it lies in the scalenus anticus, crossing that muscle from above downwards and inwards. The nerve is caught in a pair of artery forceps and divided $\frac{1}{2}$ cm. above the level of the omohyoid. The stimulation of the nerve at this point may cause pain in the shoulder, radiating down to the inner side of the upper arm, referred to the area of cutaneous distribution of C 3 and 4, or to the area supplied by the last six intercostal nerves, i. e. the hypochondrium or epigastrium. These signs are valuable in identifying the nerve, as the oedema produced by the local anaesthetic may render this difficult. When the nerve, thus identified, is caught with forceps, it requires a long steady pull to evulse it. Continental authorities advise a gradual twisting at the rate of one turn per minute at this stage. It is advisable to apply several pairs of artery forceps along the course of the nerve as a safeguard against the nerve snapping in the early stages of the evulsion before a sufficient length has been obtained. If, as a result of pleural adhesions, the nerve is densely embedded in the surrounding

tissues, there may be more resistance than is normally experienced in such a case. It is unwise to use force, as this may cause reactivation of quiescent foci, and it is better to be content with simply resecting as much as possible. When the extracted part is 12 cm. or more we can be fairly certain of having got rid of the accessory roots; much more than this is generally obtained, however, for it frequently happens that the whole nerve with its terminal roots is evulsed from the diaphragm, in which case 30 to 40 cm. are obtained. The operation thus completed the wound is closed in the usual way.

IX. *Complications.*

1. It is possible that there may be some haemorrhage from the pericardiophrenic artery, which lies with two venae comites in a connective-tissue sheath along with the phrenic nerve, which they accompany in the thorax; if the sheath is uninjured the haemorrhage soon ceases, and the haemorrhage from the veins is not dangerous. Felix (20) says it can be avoided with care in extraction, and he only saw it once in over 150 cases treated at Munich.

2. The question of haemorrhage from the subclavian vein has been discussed. The phrenic itself runs behind the subclavian vein in the thorax, while the accessory phrenic, when present, runs in front; on pulling the nerve a sling is formed in which the vein may be caught, but in the majority of cases the accessory phrenic snaps and the sling is torn (H. Alexander (1)).

3. Air embolism. This is much more frequent in the so-called radical phrenicotomy than it is in phrenic exaeresis. It can be averted by careful arrest of haemorrhage, every large vessel in the operation area being seized and ligatured. The nerve is divided above the omohyoid so as to avoid the internal jugular vein. Should air embolism occur the patient's head is lowered so as to prevent the return of blood to the right side of the heart; if available, the mask of a pressure apparatus is applied to the patient's face so as to increase the pressure in the pulmonary circulation and prevent the blood coming back from the systemic circulation to the right side of the heart.

4. Haemoptysis may occur, especially if the nerve is adherent to infiltrated lung tissue, and this becomes unduly stretched while the nerve is being pulled upon. Zadek (98) observed this in two of his cases, but in both the final results were satisfactory.

5. Reflex disturbances may occur affecting heart and respiration; precisely how they occur is not definitely known, but possibly the vagus or the intercostal nerves may play a part in their production. During the pull on the nerve the diaphragm is often raised 1 to 2 in., and falls again after division; this may cause a change in the position of the heart, affecting the pulse-rate. It is not at all uncommon to have a little dyspnoea, a rapid or a slow, weak, and irregular pulse, during the actual twisting of the nerve. In a case reported by H. Alexander (1) the reflex disturbances were so severe as to render exaeresis impossible; in another case there was a tachycardia which lasted five months.

In one of our series attacks of vomiting, apparently of reflex origin, persisted for a week following a left-sided phrenic evulsion.

6. It must be remembered that adhesions in the course of the nerve may fix it so that extraction is dangerous; cold abscess has followed when the nerve is embedded in a caseous focus (Goetze (31). Sauerbruch (77) regards the presence of a tuberculous empyema or pleural adhesions over the nerve as definite contra-indications for exaeresis, as the freeing of infectious material might cause a fatal mediastinitis.

In spite of all these probable complications exaeresis has been performed extensively at a number of clinics and no unfavourable results have been reported. Baer has used it over 100 times without mishap; Felix (20) has reported 240 cases in which it has been performed without accident; in our series no noteworthy complication was observed. It will probably become the operation of choice wherever diaphragmatic paralysis is indicated, and the risks to the patient are certainly not greater than with artificial pneumothorax.

X. *Clinical Observations.*

Up to the present time thirty-one cases, mainly of pulmonary tuberculosis and bronchiectasis, have been treated by therapeutic diaphragmatic paralysis at the North Wales Sanatorium, Denbigh. In twenty-seven of these the operation was phrenic exaeresis or evulsion; in the remaining four simple phrenicotomy. The operations were carried out by Mr. H. Morriston Davies, F.R.C.S. (Eng.), Consulting Surgeon to the King Edward VII Welsh National Memorial Association. The indications for treatment were as follows:

Basal infections in:	
1. Bronchiectasis	3
2. Fibrosis of the lung	4
3. Hydatid disease	1
4. Pulmonary tuberculosis	2
Special indications in pulmonary tuberculosis:	
1. Pneumothorax impossible	5
2. Symptomatic relief of	
(*a*) Cough	1
(*b*) Pleural pain	2
3. Preliminary to pneumothorax	1
4. Basal adhesions in pneumothorax	2
5. Preliminary to thoracoplasty	10
(Tuberculosis 7; Bronchiectasis 4.)	—
Total	31

In all (except three cases in which general anaesthesia was used) a local anaesthetic was used (novocain 0·75 per cent. with adrenalin). The patient,

as a rule, experienced little pain except during the actual operation of extraction. When the phrenic nerve is pulled upon several phenomena are generally observed:

(1) Spasmodic contraction of the diaphragm.
(2) Pain in the shoulder, radiating down the inner side of the upper arm, sometimes reaching the tips of the fingers.
(3) Hiccup is occasionally, but by no means always, present.

Length of the Nerve. The average length of nerve removed in our series was 16·5 cm. In four cases it was possible to do a complete evulsion with the terminal filaments to the diaphragm, in which cases lengths varying from 36 to 43 cm. were obtained. It was often found that it was in precisely the type of case where pneumothorax was impossible owing to adhesions that phrenic exaeresis is almost equally difficult from the same cause, and in one case exaeresis was abandoned and simple division performed, as the extraction operation might have caused unnecessary damage to the tissues adherent along the course of the nerve.

Accessory Phrenics. An accessory phrenic was observed in three cases. In two of these it ran downwards and joined the main stem close to the outer border of the scalenus anticus; in the other case rather a curious state of affairs was found. The normal phrenic nerve lay on the lateral side of the scalenus anticus muscle, which it crossed above its insertion into the first rib. With it ran another nerve, the two being closely connected in the upper part of their course. This second nerve left the phrenic in the lower part of the neck, and turned outwards across the posterior triangle. The appearance of the two nerves suggested that the normal phrenic, was absent, and that the whole of the nerve supply to the diaphragm was in the accessory phrenic which ran with the suprascapular nerve. Morriston Davies (66) records three such cases.

In three cases it was found that, although no accessory phrenic was present, the phrenic itself was joined by several small filaments, which ran upwards and appeared to come from the suprapleural plexus.

In several other cases the phrenic nerve ran entirely either to the outer or to the inner side of the scalenus anticus instead of crossing it obliquely.

Complications. Few complications were met with. Occasionally a slight degree of pain was felt over the area of cutaneous distribution of C 3 and 4 when the phrenic nerve itself was directly pulled upon. In several of the cases pain in this area and in that part of the abdominal wall supplied by the last six intercostal nerves occurred as a post-operative symptom, disappearing in a few days. In one case (on the left side) there was a tachycardia which persisted for several days; in another case (also on the left side) attacks of vomiting occurred which persisted for about a week.

Effect on the Diaphragm. The average rise obtained in the series was 4·7 cm. on the right side and 3·85 cm. on the left side, while the maximum was 8 cm. on the right side and 6 cm. on the left. Paradoxical movements were observed only in twelve cases. In many cases they are not visible if the

base of the lung is indurated and fibrotic, or if the diaphragm is adherent. Bittorf's method was found extremely valuable as a test of their presence in doubtful cases.

Clinical Results. Of thirty-one cases treated benefit resulted in twenty-four; of the seven patients who did not benefit, in three a paralysis was not obtained, while in three of the remaining four the rise was 3 cm. or less. The impression conveyed by the above series of cases is that diaphragmatic paralysis is of more value in the basal case of post-pneumonic bronchiectasis than it is in tubercle. Six cases of bronchiectasis have been so treated; in three all symptoms disappeared following phrenic evulsion; in the remaining three the intratracheal injection of lipiodol showed that the disease extended into the upper lobe, and that thoracoplasty was necessary. This was subsequently done in all three: one of these patients (a child of 3) is now practically free from symptoms which have persisted more or less since birth. In the case of hydatid disease of the lung, already described, it was found valuable in helping to occlude the cavity following the removal of the cyst.

As regards the cases of pulmonary tuberculosis treated, from the results it would appear that, speaking generally, permanent benefit is not to be expected from phrenic evulsion, independently of other measures (e.g. pneumothorax or thoracoplasty), unless the lesion is chiefly basal. Two cases of this type were treated, with beneficial results in each case. The question may be asked as to why certain cases of bronchiectasis and of pulmonary tuberculosis do comparatively well after the diaphragm has been paralysed, and why there is little effect in others which seem equally favourable types for the operation. The answer probably is that in the latter case the upper lobe is practically always to some extent involved, and this can be demonstrated by the intratracheal injection of lipiodol. This latter procedure is therefore of value in determining whether it is necessary for thoracoplasty to follow phrenic exaeresis.

In five cases phrenic exaeresis was performed because pneumothorax had failed, and some improvement followed in four. It was intended to carry out thoracoplasty in all of these cases, but this was not done, as in two cases the patients refused further operation; in two the occurrence of signs in the relatively sound lung, and in the other the onset of abdominal symptoms, contra-indicated the operation.

With regard to its use as a symptomatic measure for relief of symptoms, in one case a troublesome cough was relieved after phrenicotomy. In two cases where the indication was persistent pleural pain, in one the pain was relieved, while in the other there was no effect as a permanent paralysis was not produced (this was one of the earlier cases in which phrenicotomy alone was used).

In one case it was used as a preliminary to pneumothorax, and assisted in producing a basal collapse where otherwise the lung would have been held out by the diaphragm.

Basal adhesions in artificial pneumothorax were responsible for the operation in two cases; in one case (already quoted) successful, in the other with little

improvement in the condition, this being due to a large portion of the upper lobe remaining uncollapsed.

In ten cases it was used in association with thoracoplasty; in all it materially assisted in producing a basal collapse, and diminished the severity of the operation by rendering a complete rib resection unnecessary. When phrenic exaeresis has been performed it is generally unnecessary to resect more than the first seven ribs: whether it is necessary to resect one or more of the lower five ribs depends upon (1) the degree of basal involvement, (2) the height to which the diaphragm rises following phrenic evulsion. The clinical results have been summarized in the table on pp. 483–5.

XI. *Conclusions.*

1. By paralysing the diaphragm, and thus preventing it taking part in respiration, we can obtain rest and relaxation of the lung, which has a definite value in therapeutics. The rise in level which results causes a diminution of the capacity of the thorax from one-sixth to one-third of its volume (i. e. from 400 to 800 c.c.).

2. The most satisfactory method of obtaining a therapeutic diaphragmatic paralysis is by phrenic exaeresis or evulsion, as by this method all the varieties of accessory phrenics are also included. The operation is seldom associated with complications, and the dangers are not greater than those of artificial pneumothorax.

3. It is specially indicated in lower lobe infections, whether these are due to tubercle or bronchiectasis, following post-pneumonic fibrosis. It is an adjuvant to other methods of collapse therapy, e. g. pneumothorax with diaphragmatic adhesions, and as a preliminary to the operation of thoracoplasty. It is also of value in symptomatic treatment, for it often relieves irritating cough, pain, vomiting, and dyspnoea, all of which may be due to the pull of diaphragmatic adhesions.

4. Diaphragmatic paralysis is of greatest value where there is most fibrosis; hence the acute caseating type of pulmonary tuberculosis is likely to benefit little.

5. Adhesions, basal effusion, or a stiff fibrotic lung may prevent a satisfactory rise of the diaphragm being obtained, and in such cases phrenic exaeresis may have little effect on the course of the disease. Speaking generally, when a good rise is obtained, some benefit results unless there is very extensive involvement of the upper lobe. Clinical improvement resulting in an arrest of the disease is not likely to occur with phrenic exaeresis alone, apart from its use in conjunction with other therapeutic measures, unless the lesion is almost entirely basal.

6. Phrenic exaeresis seems to have proved that the degree of pulmonary rest and compression following paralysis of the diaphragm is an important aid in collapse therapy, and even alone effects a large measure of improvement in

selected cases; it seems probable, therefore, that in the future it will be extensively used in the therapy of intrathoracic disease.

In conclusion I wish to express my thanks to Mr. H. Morriston Davies, F.R.C.S. (Eng.), Consulting Surgeon to the King Edward VII Welsh National Memorial Association; to Dr. D. A. Powell, Principal Medical Officer; to Dr. D. W. Fenwick-Jones, Medical Superintendent, North Wales Sanatorium, Denbigh; and to Dr. H. E. Watson, Medical Superintendent, South Wales Sanatorium, Talgarth, Breconshire, for permission to use notes and radiograms of cases treated under the Welsh National Memorial Association.

I have also to thank Dr. E. I. Spriggs of Ruthin Castle for suggestions and advice.

Summary of Cases.

No.	Initials.	Sex.	Age.	Indication.	Side.	Length.	Terminal Filaments.	Accessory Phrenic.	Paralysis.	Rise.	Paradoxical Movement.	Clinical Results.
						cm.				cm.		
1	D. S.	F.	25	Basal bronchiectasis	L.	Simple division	–	—	+	—	–	Clinical result good. Symptoms relieved, especially dyspnoea
2	E. V.	F.	27	Cough and dyspnoea. Relief of symptoms	R.	Simple division	–	—	+	—	–	Symptomatic relief only: dyspnoea and cough relieved; sputum less. Died 22.3.26
3	M. D.	F.	27	Relief of symptoms. Pleural pain	R.	Simple division	–	—	–	—	–	Only temporary paralysis; no change
4	V. R.	F.	24	Dyspnoea, vomiting, basal adhesions in pneumothorax	L.	9	–	—	+	2·5	+	Clinical result good. Relief of dyspnoea and vomiting. Continues to do well
5	A. S.	M.	25	Basal adhesions in pneumothorax	R.	18	–	—	+	2·25	+	Little change in condition: dyspnoea improved. Died 13.11.26. A.P. till August, 1926
6	G. B.	F.	31	Pulmonary tuberculosis, basal lesion	R.	10	–	Suprascapular	+	4	–	Clinical result good: all symptoms disappeared. Now quiescent
7	D. R.	F.	26	Basal fibrosis; effusion	R.	13·5	–	—	+	3	–	Little change in condition. Goingdownhill. T.102–3°F.
8	M. R.	F.	28	Bilateral disease: pneumothorax impossible; basal fibrosis	L.	21	–	—	+	4	+	Some general improvement. Cough better than before
9	W. W.	F.	14	Bronchiectasis	L.	16	–	Accessory phrenic	+	5	–	Clinical result good: thoracoplasty found unnecessary. Marked relief of symptoms. Died 14.2.27. Pneumonia after influenza

Summary of Cases (continued)

No.	Initials.	Sex.	Age.	Indication.	Side.	Length.	Terminal Filaments.	Accessory Phrenic.	Paralysis.	Rise.	Paradoxical Movement.	Clinical Results.
						cm.				cm.		
10	G. L.	M.	20	A.P. impossible; preliminary to thoracoplasty	R.	9	–	—	+	3	+	Improved: attacks of haemoptysis ceased after phrenic exaeresis
11	C. B.	F.	31	A.P. impossible; preliminary to thoracoplasty	R.	16½	–	Filaments ? sympathetic	+	3	–	No change. Died after thoracoplasty
12	E. H.	F.	22	A.P. impossible; fibrosis of left lung	L.	22	+	—	+	2·5	+	Symptomatic relief only. Cough less severe
13	A. J.	M.	25	Preliminary to thoracoplasty	R.	35	+	—	+	—	–	Cough less. Still has cough and expectoration. T. 99° F.
14	W. J.	M.	30	A.P. impossible	L.	2·5	–	—	?	?	–	No change
15	G. D.	F.	17	Basal bronchiectasis	R.	43½	+	—	+	7	+	Clinical result good. Thoracoplasty avoided: cough and expectoration ceased
16	M. W.	F.	20	A.P. impossible; P.T. haemoptysis	L.	35½	+	Sympathetic filaments	+	2·5	+	Improved; haemoptysis ceased. Not well, recurrence of haemoptysis, going downhill
17	G. M.	F.	23	Febrile: pneumothorax impossible (T.B.)	R.	9	–	—	+	8	–	Improved; lassitude much less. Developed enteritis. Died 1.6.27
18	F. E. J.	F.	2	Preliminary to thoracoplasty (bronchiectasis)	L.	·5	–	—	+	5	–	Improved; cough and sputum less; temperature settled. Free of symptoms after thoracoplasty
19	T. J. P.	M.	21	Preliminary to thoracoplasty (T.B.)	R.	8	–	—	+	6	+	Improved. Condition satisfactory. Returning to work

20	R. A. O.	M.	40	Fibrosis of lower lobe: adhesions	L.	36	–	—	+	6	–	Improved; sputum less, thoracoplasty avoided. Still some pain
21	F. J. W.	M.	19	Preliminary to thoracoplasty (T.B.)	R.	$11\frac{1}{2}$	–	—	+	4	+	Clinical result good; improved markedly: thoracoplasty avoided. Right lung satisfactory, ? signs left base
22	A. A.	M.	$5\frac{1}{2}$	Preliminary to thoracoplasty (bronchiectasis)	R.	$18\frac{1}{2}$	–	—	+	4·5	+	Improved. No sputum
23	G. P.	M.	15	Preliminary to thoracoplasty (bronchiectasis)	R.	Division	–	—	+	—	–	Improved; cough and expectoration ceased
24	A. A.	M.	20	Hydatid of lung	R.	4	–	—	+	4·5	+	Clinical result good. Free of symptoms after phrenic exaeresis
25	E. W.	F.	16	Preliminary to thoracoplasty (T.B.)	L.	8	–	Accessory phrenic	+	—	+	Improved; cough and sputum less
26	M. C.	F.	10	Preliminary to thoracoplasty (bronchiectasis)	L.	17	–	—	–	3	–	Sputum less. Slight general improvement
27	H. B.	F.	22	Basal lesion (T.B.)	L.	30	–	—	+	3·5	–	Shoulder pain less. Disease quiescent on discharge. Condition much improved
28	M. J.	F.	26	Basal fibrosis of lung	R.	$7\frac{1}{2}$	–	—	–	—	–	Outline of dome cannot be made out: no change
29	A. W.	F.	37	Pain—old pleurisy	R.	$10\frac{1}{2}$	–	—	+	$4\frac{1}{2}$	–	Pain less
30	B. T.	F.	21	Preliminary to pneumothorax	L.	23	–	Sympathetic branches	+	$4\frac{1}{2}$	–	Shoulder pain relieved. Symptomatic relief. Improved
31	E. T.	F.	22	A.P. impossible; preliminary to thoracoplasty	L.	$9\frac{1}{2}$	–	—	+	$5\frac{1}{2}$	–	No change

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THE EXTENSIBILITY OF HUMAN ARTERIES[1]

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In previous papers Bramwell and Hill (1), Bramwell, Downing, and Hill (2), Bramwell, Hill, and McSwiney (3) have described a method (employing the hot-wire sphygmograph) whereby the pulse velocity in man may be measured. It has been shown that the velocity of the pulse wave in man is dependent chiefly upon the elasticity of the artery, since the pulse wave may be regarded as a wave passing along an elastic tube.

Variations in the velocity of the pulse wave are therefore due to variations in elasticity which may be considered as the resultant of two factors. First, the internal pressure inside the artery, which will change the elasticity by varying the stretch on the artery, and secondly, the constitution and condition of the wall itself. Bramwell, Downing, and Hill, investigating these factors in isolated human arteries, showed that the extensibility could be calculated by measurement of the pulse-wave velocity. This was true for any particular amount of stretch put on the artery, and, by varying the internal pressure, the extensibility at different loads could be estimated and curves constructed showing the relationship between arterial rigidity and blood-pressure. The results obtained on isolated vessels showed that the extensibility decreased with increasing age in the artery. In order that the living artery might be studied, Bramwell, McDowall, and McSwiney (4) subsequently devised a technique whereby similar relationships might be investigated in man. A sphygmomanometer bandage of known width (d) was applied to the arm and the pressure raised to p mm. of Hg: the effective pressure inside the artery immediately under the bandage, i.e. the pressure stretching the artery, is then not P, the blood-pressure as usually observed, but $(P-p)$. The velocity of the pulse waves under the bandage corresponds not to P, the diastolic pressure, but to $(P-p)$. By this method the pulse velocity was measured at all internal pressures up to the diastolic pressure. The extensibility of the artery was obtained by using the formula:

$$\begin{array}{c}\text{Velocity}\\ \text{(in metres per sec.)}\end{array} = 3{\cdot}57 \Big/ \sqrt{\begin{array}{c}\text{(Percentage increase in volume per mm. Hg}\\ \text{increase of pressure.)}\end{array}}$$

As in the case of an isolated artery, the extensibility was found to decrease as the internal pressure was increased.

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In this present investigation attempts were made first to obtain more accurate measurements of the extensibility of the artery at varying effective pressures lower than the diastolic, and secondly, to make measurements of the pulse velocity and arterial extensibility with pressures inside the artery higher than the diastolic. The velocity of the pulse wave was recorded by the use of a hot-wire sphygmograph, records being taken from the radial and carotid pulse as has been previously described.

Method.

To ensure accuracy in measurement of the pulse-wave velocity records have been taken on long strips of bromide paper so that many records might be analysed. Hickson and McSwiney (5) have shown that the pulse-wave velocity varies slightly with respiratory movements, being higher during expiration owing to the increased peripheral blood-pressure and vice versa. Respiratory movements were recorded simultaneously with the pulse waves, and measurements were then made at similar phases of inspiration and expiration. Usually three to five respiratory cycles were recorded; four readings for calculation of pulse-wave velocity being taken in inspiration and expiration respectively, and averaged. The mean of these two averages was taken as the mean velocity during the period. Even this method was not found infallible, since occasionally variations in pulse-wave velocity suggested the existence of blood-pressure waves other than respiratory ones. These are perhaps analogous to the Traube-Hering waves observed in animals.

The paper records were measured by the Elliot measuring machine, the limits of error, with a suitable tracing which gave sharp deflexions, being $\pm 0{\cdot}001$ sec.

Variations in effective pressure inside the artery were made as described previously by Bramwell, McDowall, and McSwiney, by compressing the artery under a sphygmomanometer bandage. If this be raised to a pressure p mm. of mercury, then the pressure inside the artery beneath the bandage is reduced from P, the normal diastolic pressure, to $(P-p)$ mm. Hg. We term this the 'effective pressure'. The length of the bandage (36 cm.) was much greater than that formerly employed, as in previous experiments (4) the length of artery subjected to compression was only about 12 cm. Thus almost the whole course of the brachial and radial artery was included under the bandage. Much greater accuracy in considering changes of extensibility with blood-pressure was naturally obtained because of the increased length of artery under observation.

Application of a bandage of this type gives a range of effective pressures between zero and diastolic pressure, but adoption of a 'negative' bandage enabled effective pressures greater than diastolic to be studied. This bandage consisted of a rubber-covered hollow cylindrical box into which the forearm could be slipped. Soft rubber flaps round the apertures and exerting a negligible

pressure made an air-tight junction between skin and bandage when the internal pressure was reduced. If the pressure inside the bandage was lowered $-p$ mm. then the pressure inside the artery was regarded as $P+p$ mm. Hg, the supporting effect of the tissues being neglected since they were pulled on by the negative pressure to the same extent as the arterial wall.

In calculating the results, the pulse-wave velocity for the portion of artery under observation was determined, using the formula:

$$y=\frac{l-d}{\frac{l}{x}}+\frac{d}{v},$$

where x equals the time of transmission between two points on an artery distant l from one another, and y the time between the same two points when a bandage of length d is applied. When a bandage is applied y is made of two parts:

(1) Time of transmission in the unaffected portion $(l-d)$ where velocity is $\frac{l}{x}$.

(2) Time of transmission under bandage d where velocity v is to be determined.

Therefore
$$v=\frac{d}{y-\frac{x(l-d)}{l}}.$$

The extensibility was calculated from the simplified formula of Hill and Bramwell (1):

$$\text{Extensibility}\ \left[\begin{matrix}\text{per cent. increase in volume for}\\ \text{1 mm. Hg rise in pressure}\end{matrix}\right]=\left[\frac{3{\cdot}57}{v}\right]^2.$$

The experiment was always carried out in the same manner, the subject sitting at ease in a chair with all muscles completely relaxed. A bandage with a tambour attached for respiratory records was fastened to the thorax. The wrist cuff for the radial pulse was then attached and measurements of blood-pressure, systolic and diastolic, were made by the ausculatory method before and after the experiment. In order to determine accurately the normal pulse velocity, records were obtained at different intervals during the experiment. The pressure in the bandage was released after each record was taken to obviate stasis; the applied pressures in the bandage being taken at random. The anatomical measurements were made by measuring the distance from the right sterno-clavicular joint to the points in the neck and wrist from which the two records are obtained. By subtracting one measurement from the other, the distance traversed by the pulse wave in the time which elapses between the commencement of the carotid and radial primary deflexions may be calculated. The duration of any experiment on one subject occupied approximately ten minutes.

Results.

(a) *Employing the 'positive' bandage.* If the curve of extensibility (the percentage increase in volume of the vessel with 1 mm. Hg rise in pressure) and arterial pressure be estimated from the velocity of the pulse wave at varying pressures it is found that the curve is in great measure characteristic of the individual. It is possible, however, to group such curves into more general divisions based on the shape of the curves. Such divisions might be termed (i) normal, (ii) hyper-extensible, and (iii) hypo-extensible, the classification being based on the type of individual forming the majority of the members of each division.

TABLE I.

Blood-pressure.	Before Experiment.	After Experiment.
Systolic	118 mm. Hg.	119 mm. Hg.
Diastolic	86 mm. Hg.	90 mm. Hg.

Length of artery = 62 cm. − 10 cm. = 52 cm.
Length of bandage = 36 cm.

Number.	Pressure applied (mm. Hg).	Interval Mean.	Time (secs.).	Velocity metres per sec.	Effective Pressure (mm. Hg).	Extensibility.
1	0	0·412	0·0794	6·42	86	0·31
2	10	0·421	0·081	6·40	76	0·31
3	26	0·460	0·0888	5·45	60	0·43
4	40	0·5555	0·1062	4·28	46	0·69
5	50	0·559	0·1079	4·18	36	0·73
6	60	0·723	0·1395	3·08	26	1·32
7	71	0·845	0·163	2·55	15	1·96

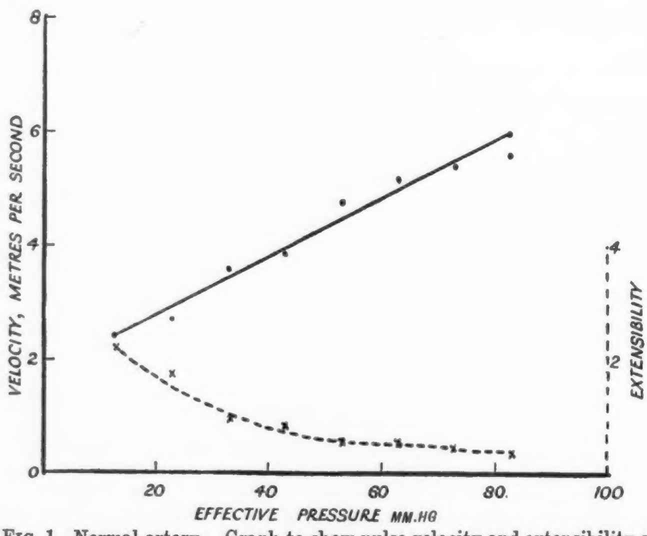

FIG. 1. Normal artery. Graph to show pulse velocity and extensibility at different effective pressures. Age 20. S. B. P. 118; D. B. P. 83. Continuous line = velocity, metres per second; dotted line = extensibility.

Table I gives the protocol of an experiment performed on an individual classed as normal, the extensibility being calculated for various effective pressures

applied through the bandage. A similar experiment is depicted graphically in Fig. 1, where the extensibility shows a steady increase with decreasing internal pressure.

Arteries in certain individuals seem to show extensibility phenomena falling definitely outside the range represented by Curve I, and according as these fall above or below the limits they have been classified as 'hyper-extensible' or 'hypo-extensible', the derivation of these terms having been previously explained.

TABLE II.

Blood-pressure.	Before Experiment.	After Experiment.
Systolic	108 mm. Hg.	102 mm. Hg.
Diastolic	83 mm. Hg.	82 mm. Hg.

Length of artery = 58 cm. − 13 cm. = 45 cm.
Length of bandage = 36 cm.

Number.	Pressure applied (mm. Hg).	Interval Mean.	Time (secs.).	Velocity metres per sec.	Effective Pressure (mm. Hg).	Exten-sibility.
1	0	0·358	0·069	6·53	82	0·296
2	12	0·386	0·0745	5·90	70	0·365
3	26	0·398	0·0768	5·70	56	0·391
4	36	0·461	0·0890	4·80	46	0·552
5	44	0·497	0·0960	4·39	38	0·663
6	55	0·605	0·117	3·50	27	1·04
7	62	0·776	0·149	2·67	20	1·79
8	70	0·979	0·189	2·03	12	3·08

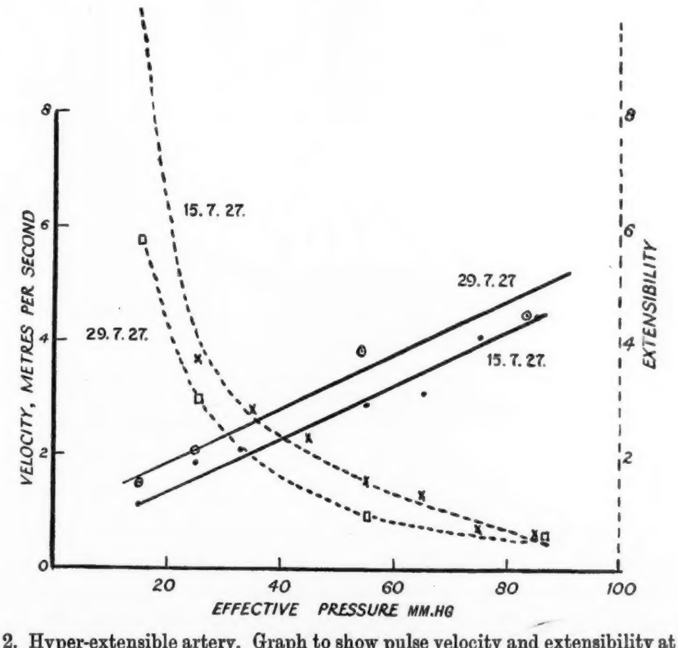

FIG. 2. Hyper-extensible artery. Graph to show pulse velocity and extensibility at different effective pressures. The two experiments were made on same subject with interval of 14 days. Age 20. S. B. P. 116; D. B. P. 85.
Continuous line = velocity, metres per second; dotted line = extensibility.

Table II gives a protocol of an experiment upon an individual of the 'hyper-extensible' type. The form is perfectly characteristic. As the internal arterial pressure falls there is an increasing extensibility with 1 mm. Hg rise in pressure. The curve begins to bend upwards sharply at 'effective' pressures below 40 mm. Hg. Thus at 38 mm. Hg the percentage increase in volume of the artery with 1 mm. rise in pressure would be 0·663, the corresponding figure at diastolic pressure (82 mm.) being 0·296. If the internal pressure be reduced to 12 mm. Hg then the extensibility becomes 3·08. Readings made on different days show such good agreement that the type of curve without doubt expresses the 'personality' of the arterial wall. Fig. 2 represents, graphically, extensibility curves obtained from another individual with an interval of fourteen days between, and showing similar form. Exact superimposition is unlikely because of the possible errors in estimating the diastolic pressure which determines the points of the abscissa.

TABLE III.

Blood-pressure.	Before Experiment.	After Experiment.
Systolic	138 mm. Hg.	—
Diastolic	92 mm. Hg.	—

Length of artery = 66 cm. − 11 cm. = 55 cm.
Length of bandage = 36 cm.

Number.	Pressure applied (mm. Hg).	Interval Mean.	Time (secs.).	Velocity metres per sec.	Effective Pressure (mm. Hg).	Extensibility.
1	0	0.366	0·0648	8·47	92	0·18
6	14	0·355	0·0684	7·76	78	0·21
5	24	0·389	0·0751	6·78	68	0·28
4	40	0·396	0·0765	6·61	52	0·29
3	50	0·430	0·0830	5·90	42	0·37
7	60	0·477	0·0921	5·14	32	0·48
2	76	0·505	0·0974	4.77	16	0·56

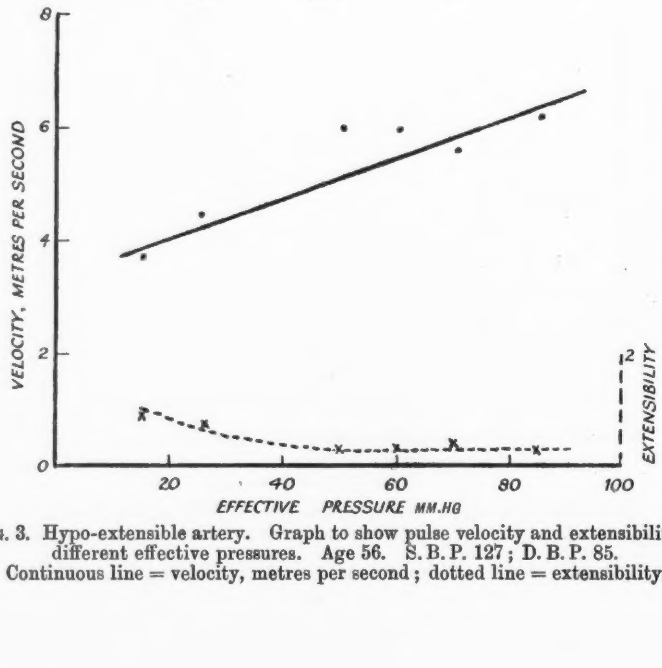

FIG. 3. Hypo-extensible artery. Graph to show pulse velocity and extensibility at different effective pressures. Age 56. S. B. P. 127; D. B. P. 85.
Continuous line = velocity, metres per second; dotted line = extensibility.

The other type of characteristic curve has been obtained chiefly from subjects of advanced years, in whom a diminished extensibility was to be expected. The extensibility factors, instead of showing a steady increase as in type (i), or an upward sweep as in type (ii), show but slight variation over the whole range of arterial pressures, indicating that the wall is almost completely inelastic. An examination of the protocol given in Table III shows a variation in percentage increase in volume of only 0·18 to 0·56, over the complete pressure range between zero and diastolic pressure, which may be contrasted with range in the average individual of 0·3 to 2·0. Fig. 3 shows results obtained from another individual.

(b) *Employment of the 'negative' bandage.* Measurements of the velocity of the pulse wave show an increased rate if the effective pressure be made greater than diastolic by the method previously described. Extensibility would appear to have reached its limit, however, for at these arterial pressures the increase in volume with unit increase in pressure is very small. The type of curve obtained is shown in Fig. 4.

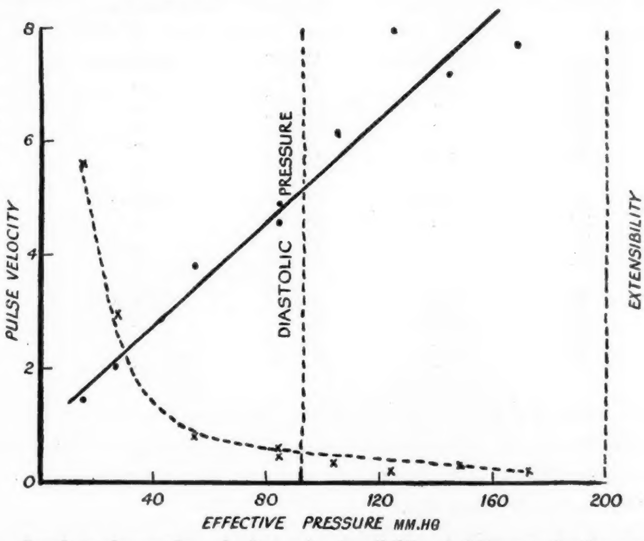

FIG. 4. Graph to show pulse velocity and extensibility at different effective pressures below (pressure bandage) and above (suction bandage) diastolic pressure. Continuous line = velocity, metres per second; dotted line = extensibility.

Discussion.

The results described above differ in certain details from previously described investigations (3) (4). Age has been regarded as the chief factor in determining the velocity of the pulse wave and consequently the extensibility of the arterial wall, but individual activities will influence and be influenced by the condition of the blood-vessels, so that an 'age grouping' cannot be expected to hold for all persons. In all the experiments performed, the form of the extensibility

curve shows a close approximation to what might be expected from the habits of the individuals. Differentiation in form is best shown in young persons, those of advancing years tending to conform to more standard activities. The divergence between this conception and the age incidence influence on arterial extensibility is probably explained by difference in tone of the plain muscle entering into the structure of the vessel wall. Presumably this may be influenced by nervous mechanisms through the vasomotor centre, so that structures with the same histological appearance may differ widely in their activity, for if we refer to the table published by Bramwell, Hill, and McSwiney, the mean extensibility of the artery at the age of 20 is given as 0·33, yet in our experiments the variation at that age is between 0·3 and 0·64, due to individuals possessing normal and hyper-extensible arteries falling in the group. In Table IV the details of the subjects examined are given.

TABLE IV.

Subject.	Age.	State of Health.	Blood-pressure.	Type of Curve.	Extensibility at Diastolic Pressure.
Male.					
1	33	Good	118/86	Normal	0·31
2	22	„	116/78	„	0·39
3	20	„	118/83	„	0·36
4	20	„	101/80	„	0·30
5	33	„	111/90	„	0·30
6	40	Fair	112/78	„	0·30
7	20	Good	116/84	Hyper	0·64
8	20	„	106/84	„	0·64
9	27	„	108/83	„	0·296
10	21	„	120/87	„	0·3
11	42	Fair	112/78	Hypo	0·25
12	56	Good	111/90	„	0·329
13	56	„	138/92	„	0·18
14	55	„	120/80	„	0·21

In the curve published by Bramwell, McDowall, and McSwiney, relating the extensibility to the effective pressure, the results obtained in different individuals were averaged. This procedure obscures the different types of response even in subjects of the same age.

It is interesting to note, on inspection of the curves, that the extensibility or percentage increase of volume of an artery per mm. increase in pressure at the normal diastolic pressure is small, and further rise of internal pressure by use of the 'negative pressure' bandage lowers this value. At lower diastolic pressures, by use of the 'positive pressure' bandage, the extensibility is increased; a gradual increase may be observed down to an internal pressure of 40 mm. of mercury. At pressures below this the extensibility is greatly increased in hyper-extensible arteries. These results appear to us to suggest that the larger arteries at normal diastolic pressure possess a low value of extensibility compared with the value at lower diastolic pressure, and with any increase in diastolic pressure these arteries become less extensible tubes. Hence, in such conditions, the

energy of the heart is expended in overcoming the rigidity of the wall and creating a high pulse pressure. This may be made clear by referring to Fig. 1, where, at an effective pressure of 40 mm. of Hg, 1·4 mm. of Hg increase in pressure leads to a 1 per cent. increase in volume, while at a high effective pressure (85 mm.) 3·2 mm. of Hg increase in pressure is required to bring about the same percentage change in volume. Vaso-constriction on one hand or vaso-dilatation on the other by altering the internal pressure will cause considerable variations in the extensibility of the arteries. On comparing the values obtained for the extensibility of the large arteries at the individual's diastolic pressure in the normal and hyper-extensible groups, which varied between 0·296 and 0·64 (see Table IV), we find that in the former subject (age 27) 3·37 mm. of Hg leads to 1 per cent. increase in volume, while in the latter (age 20) only 1·5 mm. of Hg are required. As in these two subjects degenerative changes of the arterial wall need not be considered, it appears to us that different values of extensibility observed may be due to the tone of the smooth muscle. While the large arteries do not at normal diastolic pressures exhibit their optimum extensibility, the extensibility of the arterial wall at those pressures is more than capable of dealing with the normal circulation of the body, for it must be remembered that we have expressed these values for 1 per cent. increase in volume. If the factors of pressure and volume be considered, then it will be seen that the extensibility of the large arteries is adequate.

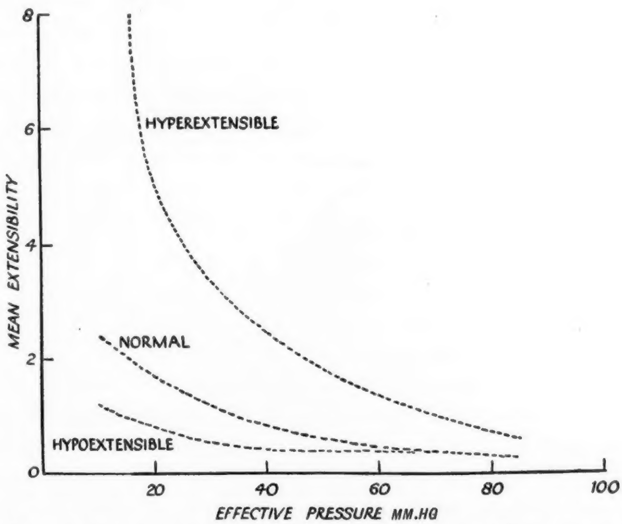

FIG. 5. Graph to show mean curves of extensibility at different effective pressures obtained in three different types of subjects.

Bramwell, Downing, and Hill found that the curve obtained on isolated arteries was similar to the composite curve obtained by Bramwell, Hill, and McSwiney on averaging the results. We find, however, that only in certain individuals do we get the same form of curve in the ranges of effective pressure

from 40 mm. to 0 mm. of mercury. The variations in extensibility obtained with the different types of arteries can well be seen in Fig. 5. It is clear that further observations must be made on isolated arteries taken from subjects of different ages with particular reference to effective pressure between 30 and 90 mm. of mercury.

Conclusions.

1. The pulse velocity and extensibility of the arteries have been measured at effective pressures ranging from 0 to 180 mm. of mercury.

2. Three different groups have been observed, which we have classified as (*a*) normal, (*b*) hyper-extensible, and (*c*) hypo-extensible.

3. Increase in extensibility of the artery is observed in all subjects at effective pressures below 40 mm. of mercury.

4. Increase of effective pressure above the resting diastolic value decreases the extensibility.

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THE HISTOLOGICAL AND RADIOGRAPHIC APPEARANCE OF INFANTILE SCURVY (BARLOW'S DISEASE)[1]

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With Plates 18–23

Scurvy rickets was very clearly described by Sir Thomas Barlow (1) in 1883. The work of recent years has separated the factor of infantile scurvy from that of rickets, and shown how the occurrence of each may be prevented. Prevention has been so successful that scurvy rickets is now a relatively rare disease in London; and it is still more rarely fatal, so that opportunities for using the improved technique of modern radiography and histology in the study of this disease are infrequent. The present paper is based on a single case, which exhibited the features of scurvy combined with rickets, and also showed in the radiography of the long bones that line of arrest of growth which is not essentially due to either rickets or scurvy, though its appearance is often misinterpreted in that sense by radiographers. The additions to the morbid anatomy, as apart from the aetiology, of scurvy rickets since the time of Barlow have consisted of various histological and radiographic reports. All the views hitherto expressed with regard to the changes at the epiphysis require re-interpretation in view of the precise changes which are now known to take place in relation to cessation of growth at the ends of the long bones. In all severe nociceptive conditions, such as the acute exanthemata, the acute respiratory diseases, diabetes, and starvation, the cartilage cells of the epiphysis cease to multiply, the columns of cells in the trabeculae are decreased in number, and the cartilaginous matrix becomes heavily calcified; bone formation therein leads to a plaque of bone in which the transverse trabeculae are crowded together and this dense plaque of bone forms an effective barrier between the relatively dormant cartilage on the one side and the normal trabeculae of bone with interspersed marrow cavities on the other. In the radiogram, as in the gross section of the long bone, this plaque of bone appears as a transverse line of cessation of growth. The occurrence of these lines of arrest of growth has been briefly

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described in previous communications (2), and their histological and radiographic development in experimental animals and in man will form the subject of a separate communication.

The experimental work of Holst and Frölich (3), of Chick, Hume, and Skelton (4), and of Delf and Tozer (5) fails to separate the three factors of rickets, scurvy, and cessation of growth. The condition which Delf and Tozer have described as chronic scurvy, in which the rows of cartilage cells are much shortened and an ossified band extends across the metaphysis, is essentially an example of cessation of growth supervening upon scurvy. The radiographic diagnosis of scurvy has been described by Lehndorff (6) and by Wimberger (7). Lehndorff showed that the 'white band' or 'Gerustmarkzone' was an area of slight shadow on the radiogram as a result of the excessive proliferation of connective tissue. On the epiphysial side of the white line or band is a band of dense shadow of variable thickness, the 'Trümmerfeldzone'. This zone of dense shadow usually has a somewhat irregular margin. It is undoubtedly due to a line of cessation of growth, and the mode of its formation will be considered.

Clinical History.

A baby boy was brought to the Out-patient Department for pain and tenderness in the feet and legs, sore spongy gums, and vomiting. The baby had been fed since birth on artificial food because his mother was sent to a sanatorium for tuberculosis. The food was Allenbury No. 2 made up with water; that is, dried cow's milk with some malted flour: no fruit juice or cream had been used. At 9½ months he had an acute attack of bronchitis, and after this began to cry when he was picked up and showed unwillingness to move the left arm and the legs. The gums became sore and were lanced by the doctor.

The child was admitted to hospital a fortnight later, when 11 months old, weighing 16½ lb. The legs were tender, the gums around the upper incisor teeth were swollen and fungating in small purple masses. There was one small palatal haemorrhage, but there were no blood-cells in the urine. The blood count showed 5,000,000 red cells per c.mm., colour index 0·66, and 9,000 white cells per c.mm. The epiphyses were not enlarged, but the radiograms showed changes at the knees and left wrist diagnosed as those of early rickets. The child was given unboiled cow's milk and orange juice, but he died seven days later with hyperpyrexia. The clinical features of the scurvy had existed for about four weeks.

Morbid Anatomy.

The autopsy revealed tuberculous meningitis as the cause of death. There was caseous tuberculous disease in the apex of the lower lobe of the left lung and in the hilum glands. Minute tubercles were found in the spleen, kidneys, and liver, and there were a few tubercular ulcers in the small intestine. The

long bones, on section, displayed broad zones of provisional calcification in the epiphysial cartilages. In the ribs and in some of the long bones this zone was irregular in shape and in continuity. Haemorrhages were seen at the costochondral junction. The bone marrow of the left femur appeared to be somewhat oedematous and gelatinous. There were no gross subperiosteal haemorrhages or other evidences of scurvy outside the bones.

The costal cartilages and ribs of the left side were cut in the coronal plane, and the sixth to the ninth ribs are depicted (Fig. 1). Naked-eye examination displays four normal tissues: cartilage, calcified cartilage of the zone of provisional calcification, bone, and red marrow. Two abnormal tissues are also seen, consisting of areas of haemorrhage on the rib side of the calcified cartilage and areas of pale gelatinous marrow between the dark area of the red marrow and the definitive costochondral junction. The zone of provisional calcification in the cartilage is seen to be markedly irregular in shape, somewhat excessive in width, and obscured to some extent in proximity to the areas of haemorrhage. There are no subperiosteal haemorrhages in relation to the shaft of the rib, but in the neighbourhood of the costochondral junction the haemorrhage tends to be more marked at the periphery, i.e. in the area of maximum torsion and stress in the rhythmically moving ribs. When a longitudinal section of the femur was compared with the longitudinal section of the ribs, it was seen by the naked eye that the red marrow was replaced by gelatinous marrow over a distance of about 8 mm. This suggests that the scurvy condition has continued over a period of time which is necessary to produce a growth of 8 mm. in the length of the shaft of the femur—about three to four months.

Radiography.

A radiogram of the excised costochondral junction (Fig. 2) shows a picture which differs widely from the normal. The ends of the ribs, which are not markedly enlarged, present that distinct 'embroidery' effect which is characteristic of scurvy. The pale lunules of the embroidery correspond to areas of haemorrhage and connective tissue, and the dense shadows correspond to more or less regular transverse striations of dense bone. The more distal irregular transverse trabeculae near the end of the rib are succeeded by a fairly distinct transverse line in the shaft of the rib, beyond which the structure of the bone is normal.

The radiogram of the excised tibia (Fig. 3) shows no rachitic irregularity, but the dense line at the end of the diaphysis immediately bordering the epiphysial cartilage is succeeded by a fine line of dense bone at a distance of about 2 mm. on the diaphysial side of the former. The fine line, lying in the bony diaphysis, is a line of cessation of growth which had occurred during some illness, perhaps the acute attack of bronchitis seven weeks previous to admission to hospital. The dense transverse line at the end of the diaphysis is the terminal line of cessation of growth as the tuberculous infection developed its fatal

miliary form. This dense transverse line is the projection of a plaque of dense bone which occupies the whole of the transverse section of the shaft on the diaphysial side of the epiphysial growth cartilage.

The two distinct lines of cessation of growth, the one fine and lying in the diaphysis, the other dense and limiting the diaphysis, are not so clearly identified in the radiogram of the ribs as in the radiogram of the tibia. In the first place it has to be remembered that the radiographic shadow of a plaque of thin bone will only appear as a transverse line of cessation of growth when the axis of the ray lies in the plane of the plaque, and the plaque itself is in one plane. With obliquity of the rays, or with an absence of flatness in the plaque, the radiographic projection will be either an ellipse or a double line of more or less wavy outline. Whereas transverse lines are commonly seen in the radiograms of the long bones at the knee and ankle, they are but rarely seen with a similar degree of distinctness at the costochondral junction, for the end of the rib is normally somewhat cupped, and in the case of florid rickets is markedly so. Also the axis of the ray rarely lies in the plane of the end of the rib. In the radiogram of the ribs (Fig. 2) a faint transverse line is seen about 2 to 3 mm. from the end of the rib. This line may correspond to the faint line of cessation of growth on the radiogram of the tibia, i.e. the line which was formed during the earlier illness. The line of cessation of growth at the end of the rib, corresponding to the dense line of cessation of growth at the end of the diaphysis of the tibia, is not so clearly demarcated. This is probably due to several factors. For not only does the ray strike the costochondral junction somewhat obliquely, but the manifestations of scurvy probably continued thereat over a longer period of time, so that haemorrhages were still occurring in this area when they had ceased at the ends of the long bones. Thus the region of provisional calcification at the costochondral junction is torn up by haemorrhage to a greater extent, the integrity of the line of cessation of growth is not so marked, and the 'embroidery' effect on the radiogram is pronounced.

Examination of the ante-mortem radiogram of the knee-joint (Fig. 4) shows the typical characters of mild scurvy rickets in the process of healing, with two lines of cessation of growth. There is a faint line of cessation of growth near the end of the diaphysis, and there is a dense line of cessation of growth at the end of the diaphysis. The bone between the two lines of cessation of growth shows but a faint shadow and is a typical 'white band' or 'Gerustmarkzone'. The dense line of cessation of growth at the end of the diaphysis, immediately contiguous to the epiphysial cartilage, is the 'Trümmerfeldzone'.

Histology.

At the costochondral junction the irregular arrangement ot the zone of provisional calcification (Fig. 1) is marked. The floridity of rickets depends largely on the degree of movement to which the joint is subjected, and so does the degree of collapse in the continuity of the calcified zone. Three sections of

costochondral junctions from various sources are given (Fig. 5) to show the appearance of the normal, syphilitic, and rachitic condition. In the normal the modelling of the cartilage and bone is economical, without redundancy of material. In the syphilitic there is some irregularity in the junction, and there are lymphocytes and fibroblasts in relation to the newly formed bone. In the rachitic junction there is an increase in the number of cells in the cartilaginous columns; the metaphysis has collapsed and become folded on itself; there is marked irregularity in the epiphysial line and marked excess of low-grade osteoid tissue. The 'beading' is essentially an enlargement of the osteoid tissue rather than of the cartilage. The section of the costochondral junction from the present case (Fig. 6) shows the characteristic feature of rickets in the elongated columns of cartilage cells, in the collapse of the epiphysial line, and in the outlying islets of cartilage cells in the bony shaft. The recently formed bone is not osteoid in character, but is dense and consolidated as a result of the terminal cessation of growth in the acute illness. The rickets has been 'healed' by cessation of growth in much the same sense as diabetes is 'healed' by starvation. The manifestations of scurvy in the section consist of areas of haemorrhage, areas of excessive development of fibrous tissue, and areas of gelatinous marrow devoid of blood-forming cells.

In the low-power view of the distal epiphysis of the femur (Fig. 7) there is but slight evidence of rickets. The distal end of the diaphysis over a zone 8 mm. in length is seen to be free from red marrow, the spaces between the bony trabeculae being filled with gelatinous tissue. The same tissue is seen near the distal margin of the centre of ossification over a band of about 2 mm. These two areas give an idea as to the amount of growth of new bone in the diaphysis and in the centre of ossification respectively since the onset of the scurvy. Increased magnification of the distal epiphysial line of the femur (Fig. 8) shows the residual areas of haemorrhage and the gelatinous character of the marrow with absence of erythroblastic and leucoblastic areas. However, in contiguity to the epiphysial line, normal marrow cells are seen, though not so plentifully as in the central portion of the shaft (Fig. 7). This is a fact of great significance in that, in the process of healing of the scurvy, normal erythropoietic marrow appears at the metaphysis in the area of the most recently formed capillaries. Thus in the scurvy the anaemia is not only due to the succession of haemorrhages, but is due to the formation of gelatinous marrow with failure of differentiation of the marrow into erythroblastic and leucoblastic areas. Moreover, the process of healing does not extend by continuity from the normal red marrow of the central portion of the shaft to the metaphysis, but arises *de novo* at the metaphysis, leaving an intermediate area of gelatinous marrow corresponding in width to the duration of the disease. Schmorl (8) indicated that the healing of rickets does not extend from the normal trabeculae of the diaphysis to the epiphysial line, but commences there where normal ossification would be occurring if no rickets had been present. Similarly, in the healing of scurvy, the formation of normal marrow occurs there where

normal marrow would be formed if no scurvy had been present. This is a clear indication that the process of healing both in scurvy and rickets is not dependent on extension of the normal tissue, but on a special differentiation *in situ* as a result of blood-borne substances. It is this feature of the healing process which accounts for the radiographic and histological findings in healed scurvy no less than in healed rickets.

The narrow band of gelatinous marrow in the centre of ossification at the lower end of the femur (Fig. 7) is seen to be situated on the side away from the epiphysial line. The margin of the centre of ossification towards the epiphysial line serves as a fixed line of no growth, whereas the margin away from the epiphysial line gradually extends distally. Irregularities of growth in the small bones of the carpus may be evidenced by concentric circles, but in the ossification centres of the epiphyses of the long bones such circles are always eccentric, and are in contact over a flattened area which borders the epiphysial cartilage. This is in accord with the view expressed by Reyher (9).

The Line of Arrested Growth and the Line of Healing Rickets.

Parsons (10) has recently suggested that the transverse striations of bone represent a period in which better bone is laid down as a result of improvement in the general condition, rather than as an indication of arrest of growth. Lehmann (11) says, in a description of coeliac disease, 'In the distal epiphyses of the radius and ulna there is also to be seen a stratification consisting of multiple horizontal lines, so-called "year rings". These year rings seem suspicious of past rickets. They are no proof of it, however, since they occur in other nutritional disturbances of bone.' Hess (12) says that 'the explanation of the development of these transverse lines has always been lacking'.

In order to indicate clearly the characters of the two lines, the one of healing rickets and the other of arrested growth, longitudinal sections (Fig. 9) are shown of the tibia in three rats of the same litter, all three having been rendered rachitic. The first rat was killed with the rickets untreated, the second had received irradiated cholesterol, and the third had been confined to a diet of nothing but water for four days. In the first case the rachitic epiphysial zone is much wider than normal, in the second case the epiphysial cartilage is restored to its normal width by the intercalation of the line of healing rickets, and in the third case the end of the diaphysis is occupied by a dense plaque of heavily calcified cartilage and dense bone which is of considerable thickness. The epiphysial cartilage has almost disappeared, so that the arrest of growth is almost comparable to that seen in the final cessation of growth in the adult animal.

The first radiogram in Fig. 10 illustrates the lines of cessation of growth seen in the case of repeated attacks of broncho-pneumonia with bronchiectasis in a non-rachitic child who had received cod-liver oil continuously from birth. The second radiogram shows the line of healing rickets following upon the

administration of cod-liver oil in a child with florid rickets. The line of healing rickets is always bounded on the one side by an epiphysial cartilage of normal width, and on the other by an area of metaphysis in which there are varying amounts of proliferated cartilage, osteoid tissue, and recently formed bone according to the stage of healing. The line of cessation of growth at the time of its formation is always bounded on the one side by an epiphysial cartilage in which the number of cartilage cells in the trabeculae is reduced by reason of decreased rate of proliferation, and on the other side by a normal metaphysis in which the bone and marrow are fully differentiated. In the case of healing rickets the bony trabeculae laid down in the metaphysis are abnormal and irregular, and are not remoulded to form trabeculae of normal appearance for many months. In the case of lines of arrest of growth the trabeculae in the metaphysis are usually normal, unless one is dealing with a case of arrest of growth as the result of acute disease in a case that exhibits or has recently exhibited rickets.

Vegetative Proliferation and Differentiation for Function.

In cases of scurvy rickets it is essential to note the histological as well as the radiographic picture. The anaemia of scurvy is the product not only of the haemorrhages but also of the failure of the bone marrow to form normal erythropoietic areas. Stump (13) has recently stressed the identity of the embryonic cells which give rise to the chondroblasts, the endothelial cells of the capillaries, and the primitive haemoblasts of the bone marrow. The processes which lead to the differentiation of the various tissues depend upon the presence of certain vitamins. The proliferation of the cartilage at the epiphysial line depends upon the presence of water-soluble vitamin B. This is a typical vegetative process comparable to the proliferation of bacteria, cambium cells, or tumour cells. The calcification of cartilage depends upon the presence of fat-soluble vitamin D, which is identical with the ultra-violet factor in irradiated cholesterol or ergosterol. This process is comparable to degeneration and calcification in a gumma, tubercle, or fibroid. The differentiation of the osteoblast depends upon the presence of blood-borne fat-soluble A, and the differentiation of the haemoblasts of the marrow depends upon some closely allied or identical substance. The impermeability of the capillaries to blood, as distinct from lymph, depends upon the presence of water-soluble vitamin C.

In the case of scurvy it has yet to be ascertained to what extent the gelatinous marrow, closely resembling embryonic mesenchyme, is dependent upon the lack of blood-borne substances of a vitamin-like nature. Further, it is still impossible to assess the extent to which this primitive connective tissue in the gelatinous marrow results from the healing of the haemorrhagic areas. The recent work on the varying responses in the blood marrow in cases of pernicious anaemia and of secondary anaemias in response to a diet of liver on the one hand, and a diet rich in vitamin A on the other, suggests certain aspects.

Much more detailed experimental work is necessary in order to distinguish the factors governing purely vegetative phenomena of cell-proliferation as seen in cartilage and gelatinous marrow from the antagonistic phenomena of cell-differentiation for specific function as seen in bone and red marrow. It may be that fat-soluble vitamin A is not the only vitamin concerned with processes of cell-differentiation for function, and that water-soluble vitamin B is but one of many substances concerned with vegetative proliferation or growth.

Conclusions.

1. In a case of scurvy rickets, the formation of gelatinous marrow, with the failure of normal erythropoiesis, is shown to be an essential part of the resulting pathological picture, and of the anaemia in particular.

2. No case of scurvy rickets can be completely analysed in terms of scurvy and rickets without due attention being paid to the phenomena associated with arrest of growth. The so-called chronic scurvy always displays these phenomena in a marked degree, and the 'Trümmerfeldzone' is essentially a line of cessation of growth.

3. The process of healing in scurvy has certain features in common with the process of healing in rickets, especially as regards the site of the healing. The site of healing is juxta-epiphysial and arises *de novo*, not by extension from the normal bone and marrow of that part of the diaphysis which was formed before the onset of the disease.

4. The line of arrested growth exhibited during acute diseases, infectious, respiratory, or metabolic, is identical in its genesis with the line of arrested growth exhibited in normal physiological cessation of growth on the attainment of adult stature.

5. The line of healing rickets can be clearly distinguished from the line of arrested growth by its site of origin and by the histological character of the neighbouring tissues. Briefly, the former is unorganized calcified cartilage, the latter is organized living bone, in which the transverse trabeculae are over-developed.

I am indebted to Dr. Barnard, pathologist at University College Hospital, for the section of the distal epiphyses of the femur. Mr. Pittock and Mr. Melville have rendered invaluable technical assistance.

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DESCRIPTION OF PLATES.

PLATE 18, FIG. 1 (with key). *Scurvy Rickets.* Section of the ribs and costal cartilages in the case of scurvy rickets.

From left to right the tissues are:

1. Cartilage of the rib (white).
2. Zone of provisional calcification (continuous lines).
3. Areas of haemorrhage (black).
4. Areas of recently formed marrow (white).
5. Areas of gelatinous marrow (dotted lines).
6. Areas of normal red marrow (white).

FIG. 2. *Scurvy Rickets.* Post-mortem radiogram of the ribs and costal cartilages shown in Fig. 1, to indicate the typical 'embroidery' effect of scurvy rickets and lines of arrested growth.

PL. 19, FIG. 3. *Scurvy Rickets.* Post-mortem radiogram of the right tibia showing two lines of arrested growth:

(*a*) Dense line at the end of the diaphysis, contiguous to the epiphysial cartilage, formed during the terminal illness.

(*b*) Fine line, 2 mm. from the former, in the diaphysis, and formed during a previous illness.

FIG. 4. *Scurvy Rickets.* Ante-mortem radiogram of the knee showing:

(*a*) Terminal dense line of arrested growth identical with the 'Trümmerfeldzone'.

(*b*) Fine line of arrested growth in the diaphysis, formed during a previous illness.

(*c*) The intervening pale area or 'Gerustmarkzone'.

PL. 20, FIG. 5. Microphotographs of the costochondral junction in:

(*a*) Normal babe.

(*b*) Congenital syphilitic (still-born).

(*c*) Florid rickets (monkey).

PL. 21, FIG. 6. *Scurvy Rickets.* Microphotograph of a portion of the costochondral junction showing the rachitic irregularities and the dense bone of the 'Trümmerfeldzone'.

Fig. 7. *Scurvy Rickets.* Microphotograph (low power) of the distal epiphysis of the femur showing:

(*a*) Normal red marrow.

(*b*) Gelatinous marrow.

(*c*) New formation of red marrow in contiguity to the epiphysial line (*e*).

(*d*) Gelatinous marrow at the distal margin of the centre of ossification.

Fig. 8. Microphotograph (higher power) of the distal epiphysis of the femur showing the character of the gelatinous marrow (*b*) with islets of haemorrhage (*f*).

Pl. 22, Fig. 9. Longitudinal section of the tibia of three rachitic rats of the same litter:

(*a*) Untreated rickets (stained $AgNO_3$) with marked increase in the width of the epiphysial cartilage.

(*b*) The line of healing rickets (H R), clearly demarcating the true epiphysial cartilage, after treatment with irradiated cholesterol (stained $AgNO_3$).

(*c*) The line or plaque of arrested growth (A G) following four days' starvation, with cessation of growth of the cartilage and almost complete union of the epiphysis.

Specimen cleared in oil of wintergreen.

Pl. 23, Fig. 10. Radiograms to illustrate the different topographical relations of:

(*a*) Lines of arrested growth formed during repeated attacks of broncho-pneumonia in a girl from the third to the eighth year.

(*b*) The line of healing rickets in a girl aged 16 months, in whom the florid rickets had been treated daily with two drachms of cod-liver oil for two weeks.

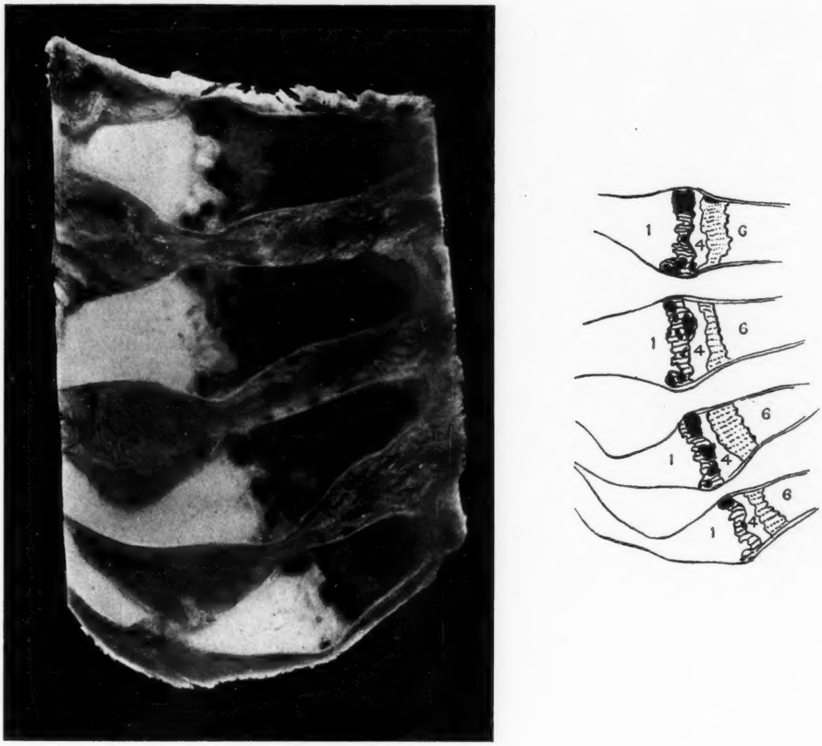


FIG. 1

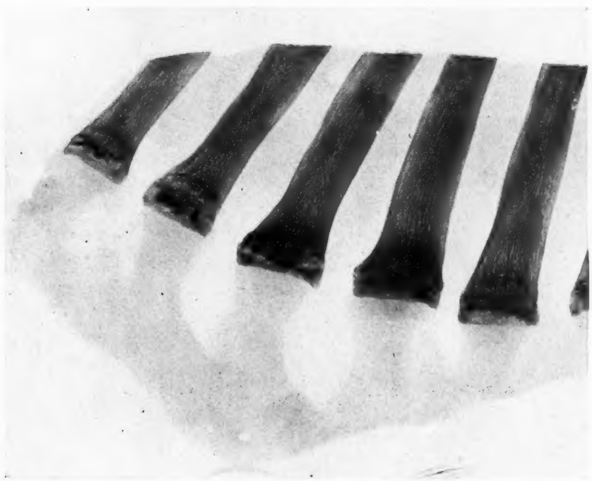


FIG. 2

FIG. 3

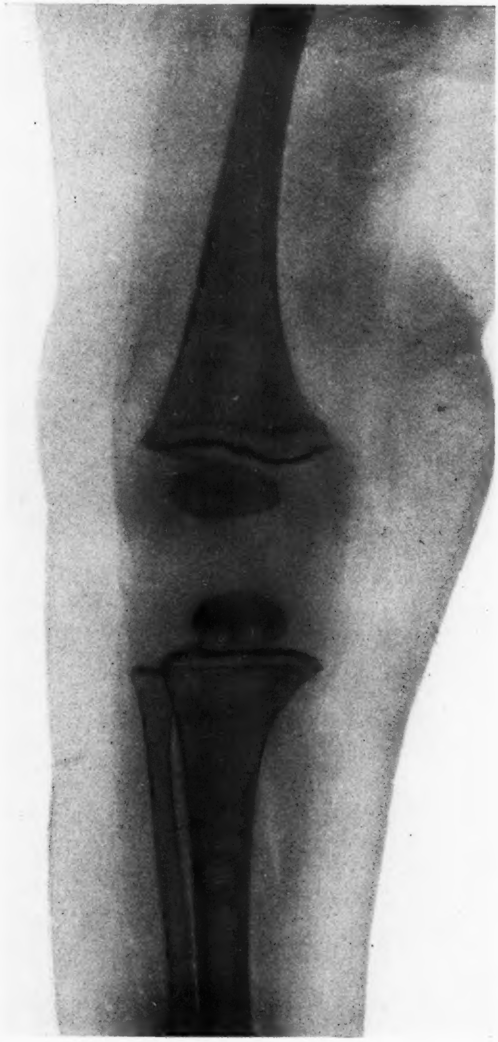
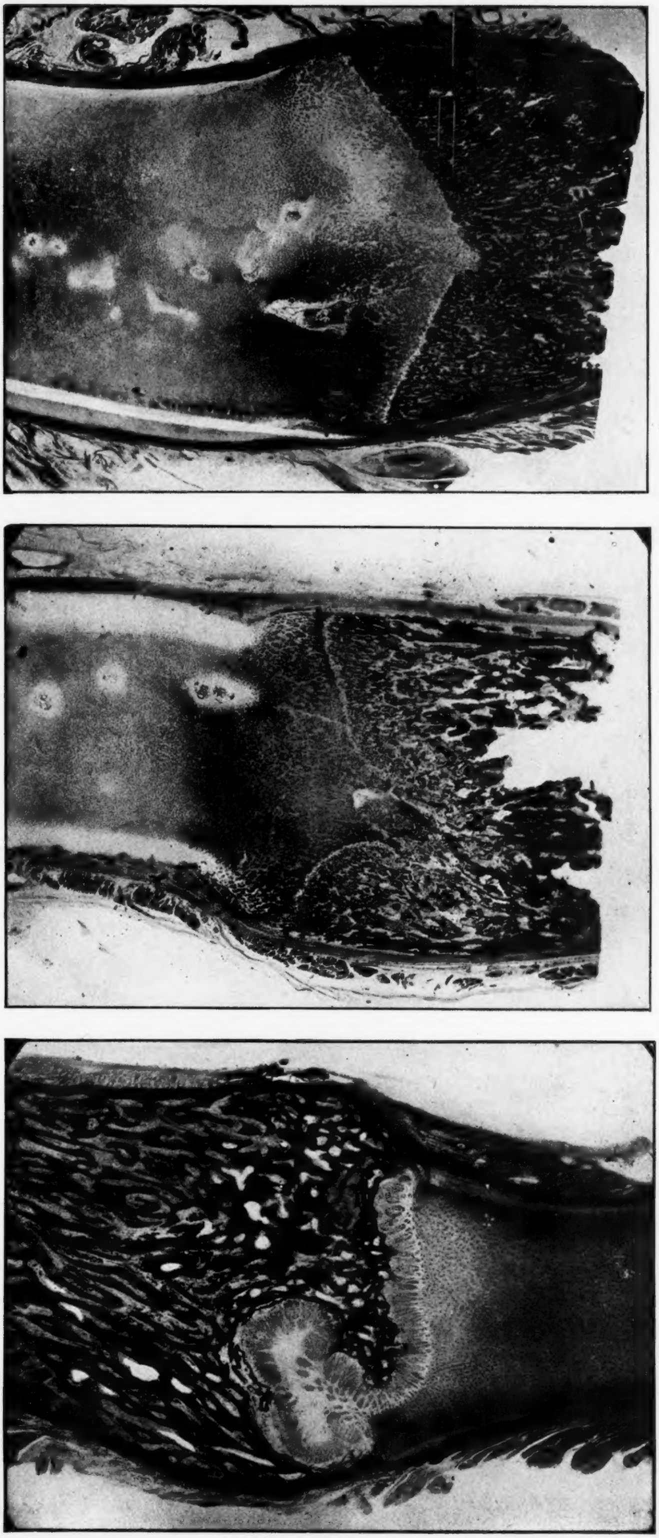


FIG. 4



a

b

c

FIG. 5

Fig. 6

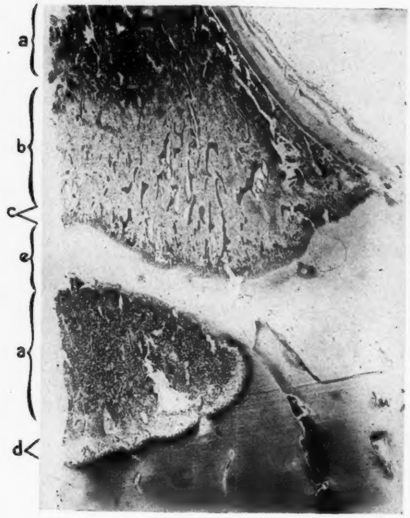


Fig. 7

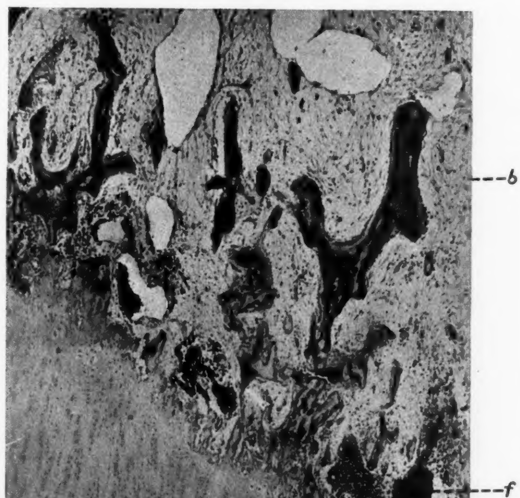
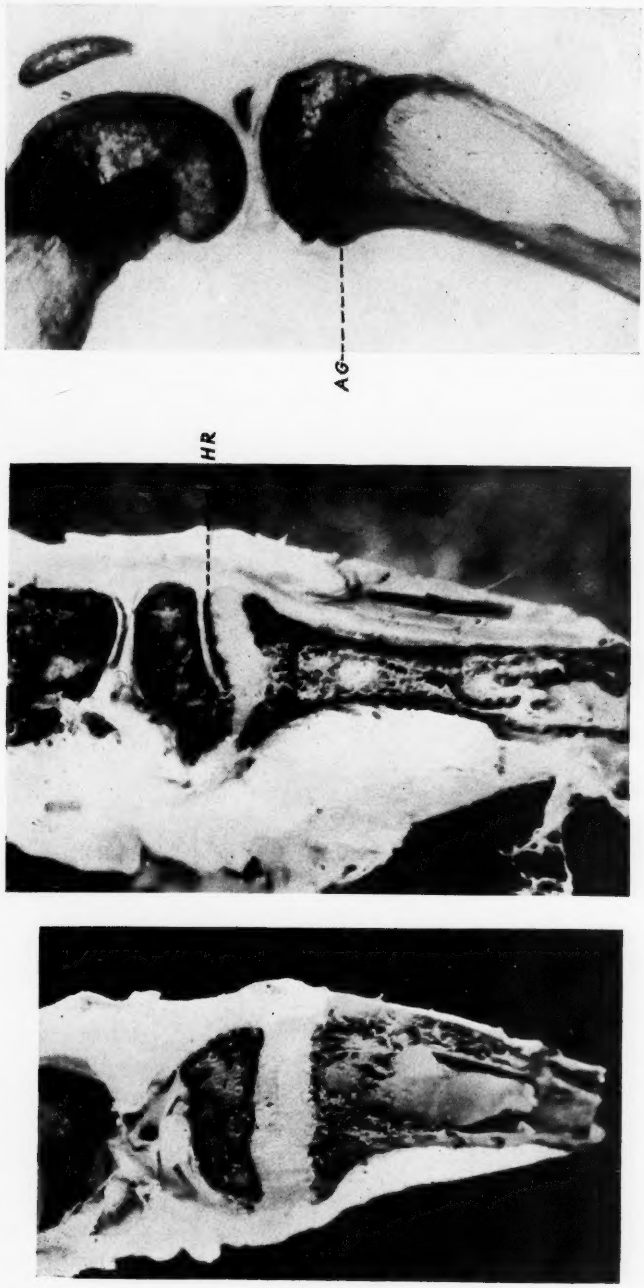


Fig. 8



c

b

a

FIG. 9

a

b

Fig. 10

THE USE OF SYNTHALIN IN THE TREATMENT OF DIABETES MELLITUS [1]

BY GEORGE GRAHAM AND G. C. LINDER [2]

(From the Wards and Laboratories of the Medical Professorial Unit, St. Bartholomew's Hospital)

THE natural desire for a remedy which can be taken by mouth and thus replace insulin has been partly responsible for the introduction of synthalin. It owes its discovery to the following observations, which had nothing to do with diabetes mellitus. Noel Paton and Findlay (1) thought that parathyroid tetany was connected with guanidine poisoning. Underhill and Blatherwick (2) believed that hypoglycaemia was connected with tetany, and Watanabe (3) found that the blood-sugar of animals who had been poisoned with guanidine was very low. Frank (4) confirmed this observation, and showed that the blood-sugar of a fasting rabbit fell from over 100 mg. per cent. to 50 or 35 mg. per cent. in four or five hours, and that the animals died in convulsions which had some resemblance to those caused by insulin. Its effects differed from those of insulin, since the animals did not recover when sugar was given, and even if ample carbohydrate was given before the guanidine the animals lived for only thirty-six hours. If the dose of guanidine was so small that it did not kill the animal, the blood-sugar remained unaltered. Guanidine itself could not therefore be used for the treatment of patients because of its toxic properties, so Frank, Nothmann, and Wagner (5) tried the actions of various substitution products. Agmatine (aminobutyleneguanidine)

$$NH_2—\overset{\overset{NH}{\|}}{C}—NH—CH_2—CH_2—CH_2—CH_2—NH_2$$

caused a fall in the blood-sugar and less toxic symptoms. A further increase in the side chain, aminopentyleneguanidine

$$NH_2—\overset{\overset{NH}{\|}}{C}—NH—CH_2—CH_2—CH_2—CH_2—CH_2—NH_2$$

was also effective. The best results so far have been obtained with a substance which has two molecules of guanidine joined together by 10 CH_2 groups,

$$NH_2—\overset{\overset{NH}{\|}}{C}—NH—CH_2—(CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2)—CH_2—NH—\overset{\overset{NH}{\|}}{C}—NH_2.$$

[1] Received March 16, 1928.

[2] Working with the assistance of a grant from the Medical Research Council.

This substance has been called synthalin. It has been tried extensively on animals, and also on patients with and without diabetes mellitus. It does cause a fall in the blood-sugar of fasting animals, and its toxic effects are not nearly so severe as those of guanidine.

Frank, Nothmann, and Wagner found that the dose of synthalin necessary to cause a definite fall in the blood-sugar was 0·003 grm. per kilo of body-weight in young rabbits compared with 0·03 grm. per kilo for agmatine. They believed that the sugar was taken up by the muscles in some way, for when synthalin was injected into the artery of a limb, the blood-sugar in the vein became slightly lower than that in the artery (10 mg.). They were able to lower the blood-sugar and to produce hypoglycaemia in a completely depancreatized dog, but if convulsions occurred the dog either died at once in spite of sugar, or was very ill and liable to die in the next few days.

The observation that sugar disappeared from the blood raised the hope that it might be burned or stored in the muscles, or elsewhere in the body. The best test of this would be obtained by perfusion of an eviscerated cat, preparation by the methods employed by Burn and Dale (6), and Best, Hoet, and Marks (7) in the corresponding case of insulin. All the sugar which disappeared under the influence of insulin was accounted for as having been burned or stored as glycogen. Staub (8) has attempted to carry out similar experiments with synthalin. He used rabbits instead of cats, and also removed a large part of the livers. The experiments were difficult to carry out, as a large dose of synthalin had to be given in order to get a result within the time of the experiment, and the animals were made very ill. He found that although sugar did disappear from the blood, there was actually a decrease in the glycogen of the muscles. At the same time there was a decrease in the oxygen consumption. This suggested that the glycogen might have been converted into lactic acid, and a considerable increase in the lactic acid content always occurred.

Bodo and Marks (9), working independently of Staub, have used the original Burn and Dale technique. They also found the decrease in the blood-sugar, the decrease in the glycogen in the muscles, and the decrease in the oxygen consumption. They likewise found a considerable increase in the lactic acid content of the blood, but observed that the lactic acid decreased after a time. So far they have no evidence of the fate of the lactic acid.

These experiments are very important in demonstrating that the action of synthalin is fundamentally different from that of insulin, and that it lacks the essential power of endowing the organism with the ability to oxidize glucose. Whether the body is able to use the lactic acid which has been formed has not been discovered so far. It must be observed that both Staub and Bodo and Marks used much larger doses than Frank, Nothmann, and Wagner, and it is possible that the toxic action of synthalin predominated in their experiments.

Observations on the respiratory quotient have been difficult to make, owing to the long delay which occurs before synthalin produces any action. A rise of

respiratory quotient in man has not been observed, except in one case by Calvert (26).

It has been suggested that a large part of the action of synthalin may be accounted for by an action on the liver, depressing its function of deaminizing amino acids, in which process a quantity of glucose is formed. Blatherwick, Sahyun, and Hill (10) showed that in rabbits synthalin decreased the rate of deaminization of glycine.

On patients, Frank, Nothmann, and Wagner got good results. The sugar disappeared from the urine of patients with mild diabetes, and the blood-sugar was lowered although not reduced to normal. In patients with a severe form of the disease, the dose of insulin could be considerably reduced, and it was also of assistance for patients with gangrene of the leg. It could not be used in patients who were in coma, as it did not produce its action quickly enough, and it was not recommended for children. The amount of acetone bodies in the urine was diminished or completely abolished. Synthalin, however, possessed some toxic properties; as it might cause nausea, epigastric pain, loss of appetite, and vomiting. In order to avoid the toxic effects, Frank recommended that it should be given for three consecutive days and then omitted for one day, so as to allow the evil effects to pass off. In spite of these precautions some patients complained of the above symptoms, and two patients developed jaundice, and one died as the result of continuing the drug (Adler (11)). In order to avoid these evil effects Adler has used sodium dehydrocholate (trade name decholin).

The early reports by Richter, Umber, Rosenberg, Strauss, von den Velden, Klemperer (12), were all very favourable, and Adler (11), Nissel and Wiesen (13), and Arndt, Müller, and Schemann (14), all had similar results. Joslin (15) and Rabinowitch (16) had some good results, and the same is true of Graham and Linder, Leyton, Maclean, Langley and Garfield Thomas, and Murray Lyon (17), although they are none of them enthusiastic and have all seen bad toxic symptoms. In Germany, Jansen and Baur (18) had very poor results, while Merklen and Wolf (19) thought it had no action. In this country Packer (17) got no action, and Lawrence (17, 21) found it quite inactive in his first series of cases, but later, while comparing the action of glukhorment and synthalin, found that a definite lowering of the blood and urinary sugar occurred.

The first accounts of the action of synthalin seemed of such interest that we, in common with six other workers, were asked by the Medical Research Council to test its effects on patients. A preliminary report has been published (17), and reference has also been made to the work (22). The present paper gives the more detailed account of our share in this investigation together with the after history of the patients treated.

We found it a little difficult to obtain suitable material, as many patients who were already having insulin were unwilling to come into hospital unless we could promise them a real advantage and that synthalin would work as well as insulin. We tested the drug on five patients who had recently reported at the

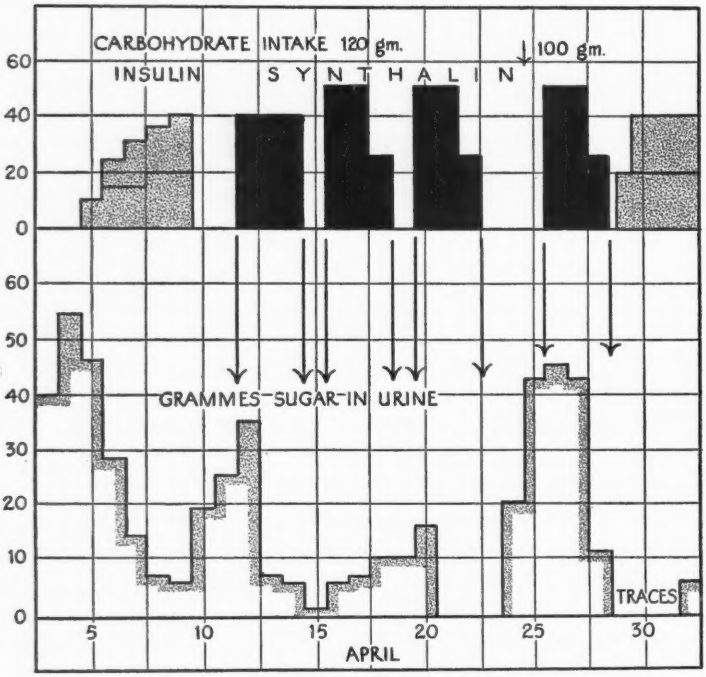

CARBOHYDRATE INTAKE 120 gm.
100 gm.
INSULIN
S Y N T H A L I N
60
40
20
0
60
50
40
30
20
10
0
GRAMMES SUGAR IN URINE
TRACES
5
10
15
20
25
30
APRIL

Fig. 1.

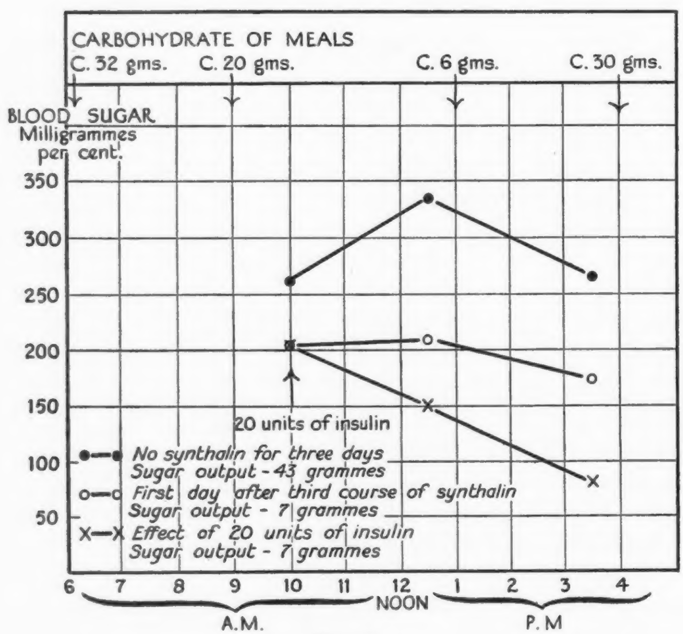

CARBOHYDRATE OF MEALS
C. 32 gms.
C. 20 gms.
C. 6 gms.
C. 30 gms.
BLOOD SUGAR
Milligrammes per cent.
350
300
250
200
150
100
50
20 units of insulin
No synthalin for three days
Sugar output - 43 grammes
First day after third course of synthalin
Sugar output - 7 grammes
Effect of 20 units of insulin
Sugar output - 7 grammes
6
7
8
9
10
11
12
NOON
1
2
3
4
A.M.
P.M

Fig. 2.

hospital, and on seven who had been taken in either because they were unwell, or specially for synthalin treatment.

The treatment was begun in hospital under the supervision of a staff accustomed to the care of diabetic patients, and the latter were kept in bed. The diet used was based on the ladder diet (Graham (23)) with extra carbohydrate in the form of milk, fruit, and sometimes bread, according to the patient's wishes. The urine was collected every three hours and tested qualitatively for sugar, and if sugar was present in any considerable amount the total output for the day was estimated. The blood-sugar was estimated at frequent intervals, and sometimes throughout the day without interrupting the normal routine of meals, specimens being taken at 9 a.m., 12.30 p.m., 3 p.m., and 5 p.m. Owing to the hour at which the patients started their day, it was not possible to estimate the fasting value of the blood-sugar without upsetting their routine diet.

The Action of Synthalin.

Case I. In order to demonstrate the action of synthalin a patient was chosen who had a mild form of diabetes mellitus. The diet contained 120 grm. carbohydrate (C.), 81 grm. protein (P.), 130 grm. fat (F.). On this diet he excreted between 40 and 56 grm. of sugar, and the blood-sugar at 10 a.m. was always above 250 mg. A dose of 20 + 20 units of insulin reduced the sugar output to 6 grm., and the blood-sugar at 10 a.m. was about 220 mg. per cent., and decreased in the usual way after the insulin (Fig. 1). When the insulin was omitted for two days the urine-sugar rose to 25 grm.

The first course of synthalin, 20 mg. twice a day, reduced the glycosuria to 6 grm., and lowered the blood-sugar on the morning of the third day to 180 mg. per cent. The blood-sugar at 12·30 p.m. was rather higher, 190 mg. per cent., but had fallen to 140 mg. per cent. at 3.30 p.m. in spite of the usual meals having been eaten.

The second course did not produce quite such a good result, but the third course was more successful as the urine contained only a faint trace of sugar. The synthalin was then omitted for three days, and the urine-sugar rose to 44 grm. A fourth course of synthalin lowered the sugar again to a mere trace on the day after the course.

The blood-sugar was estimated at 10 a.m., 12.30 p.m., and 3.30 p.m. on several occasions in order to show the changes with insulin and synthalin and no drugs (Fig. 2). The meals were eaten at the same time each day, and 32 grm. of carbohydrate were taken at 6 a.m., 20 grm. at 9 a.m., and 6 grm. at 12.30 p.m. The dose of insulin or synthalin was taken immediately after the blood was collected, about 10 a.m. Insulin, 20 units, caused a characteristic effect, as the blood-sugar fell from 205 mg. per cent. to 150 mg. per cent. at 12.30 p.m. and to 80 mg. per cent. at 3.30 p.m. The synthalin effect was observed on the first day after the third course. The initial blood-sugar was the same as with insulin, and it was still at the same level, 205 mg. per cent., at 12.30 p.m. and had fallen to 170 mg. per cent. at 3.30 p.m. Two days later, when no insulin or synthalin had been taken, the initial point was 260 mg. at 10 a.m., and the blood-sugar had risen to 330 mg. per cent. at 12.30 p.m., and had only fallen to 265 mg. per cent. at 3.30 p.m. The difference between the curve on the first day after a course of synthalin and three days after is so great, that it is clear that the synthalin had enabled the sugar to be dealt with in some way.

Although the synthalin produced an action very similar to that found by Frank, no further tests were made on this man as he was anxious to get back to work as soon as possible. A fast of one day's duration was given, with insulin and diet gradually increased to 50 grm. C., 80 grm. P., 120 grm. F. On this diet he required 18 + 18 units to keep the blood-sugar below 130 mg. per cent. before the dose of insulin.

Case II. A woman, aged 57, was taking 110 grm. C., 60 grm. P., and 100 grm. F. On this diet she excreted sugar in every specimen of urine, and the blood-sugar was above 200 mg. per cent. Two courses of synthalin were given, and she ceased to excrete any sugar in the urine. A sugar tolerance test was made before the synthalin was given. The dose of 50 grm. of dextrose sent up the blood-sugar from a fasting value of 150 mg. per cent. to 200 mg. per cent. after thirty minutes, and it steadily rose until it was 290 mg. per cent. at the end of two hours when the observations ceased. In the first hour 0·3 grm. of sugar was excreted in the urine; in the second hour 2·3 grm.; and in the

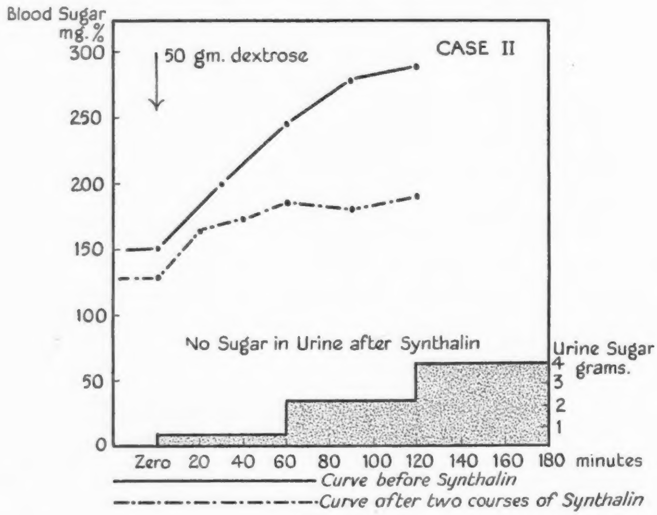


FIG. 3.

third hour 3·9 grm. The sugar tolerance test was repeated on the first day after the second course of synthalin. The fasting value was lower at 130 mg. per cent., and the blood-sugar only rose very slowly and reached its maximum, 190 mg. per cent., 60 minutes after the sugar, and had fallen slightly to 180 mg. per cent. after 120 minutes. No sugar was excreted in the urine.

The results in this case also seemed very good, but the synthalin was not continued as a reduction of the diet to 60 grm. C. controlled the blood-sugar and glycosuria quite well. She has kept very well.

The observations on these two patients convinced us that synthalin had a very definite effect in lowering the blood- and urine-sugar and therefore deserved a further trial. In these first two cases a large carbohydrate diet had been given in accordance with Frank's practice. We realized that it was difficult under these conditions to lower the blood-sugar to normal. For further observa-

tions, patients were chosen whose blood-sugar, with one exception, had been reduced to within normal limits by means of insulin.

Satisfactory Results.

Synthalin has proved very satisfactory in two cases and is still being used after nine months.

Case III. A man, aged 53, was having a diet of 35 grm. C., 65 grm. P., 110 grm. F. The blood-sugar was kept within normal limits with 25 + 25 units of insulin. Synthalin, 25 mg. twice a day, in three-day courses, was given, and the insulin was reduced to 10 + 10 units by stages. This has now been reduced to 10 + 8 units, while the carbohydrate is now 55 grm.—an increase of 20 grm. After six months the synthalin was omitted for seven days. The blood-sugar was still normal at 11.30 a.m., after three days, but after seven days had risen to 220 mg. per cent. The synthalin was restarted, and seven days later the blood-sugar was 80 mg. per cent. The man's condition is much improved, and he has gained 14 lb. in weight.

Case IV. A woman, aged 54, was having 32 grm. C., 65 grm. P., and 120 grm. F. During the previous six months she had had 15 units of insulin in one dose, and the blood-sugar varied between 100 and 200 mg. in the course of the day, but no sugar was excreted. Synthalin, 25 + 25 mg. daily, in three-day courses, was started, and the insulin was rapidly reduced. She has not had any insulin for six months, and her general condition is good. The blood-sugar varies between 110 and 170 mg. per cent. at 11 a.m., but her weight has remained steady. After ten days without synthalin the blood-sugar was 200 mg. per cent.

The results in these two cases were very striking and showed that synthalin could replace 15 to 30 units of insulin, and the blood-sugar could be kept within normal limits.

Satisfactory Results spoilt by Toxic Symptoms.

Case V. A woman, aged 32, who on a diet of 30 grm. C., 65 grm. P., 100 grm. F., required 35 + 30 units to keep the blood-sugar within normal limits in hospital. Synthalin, 25 + 25 mg., enabled the dose of insulin to be reduced to one dose of 20 units, a reduction of 45 units. After the seventh course she complained of nausea and anorexia, and asked to be given insulin again. The dose of insulin was therefore increased, and now, four months later, she has a normal blood-sugar but requires 40 + 38 units of insulin at home.

Case VI. A boy, aged 16, who on a diet of 40 grm. C., 61 grm. P., and 120 grm. F., required 15 + 15 units of insulin to keep the blood-sugar normal. A single dose of 25 mg. of synthalin was given daily, in three-day courses, and both doses of insulin were gradually reduced and then abandoned. The blood-sugar remained within normal limits and the boy continued treatment as an out-patient. He had slight nausea after leaving hospital, and the synthalin was given for only two days at a time. The blood-sugar at 11 a.m. was below 130 mg. per cent. until after the twentieth course, but then rose to 200 mg. per cent. After $4\frac{1}{2}$ months he had nausea and vomiting, and the synthalin was stopped. Insulin was restarted, and the blood-sugar was reduced to normal at 11 a.m. with 18 + 18 units of insulin.

TABLE I.

Case.	Age.	Course of Synthalin.	Insulin.	Carbohydrate. Intake.	Carbohydrate. Excretion.	Daytime Range of Blood-sugar.	Remarks.	Economy of Insulin.
			Units.	grm.	grm.	mg. %.		Units.
III	53	None	25+25	35	0	60-80	—	—
		30th	10+8	55	0	70	8 + 8 is too little insulin	32
IV	54	None	15	32	0	70-110	—	—
		20th	0	—	0	110	—	15
V	32	None	35+30	30	0	80-180	—	—
		4th	20	—	0	80-180	Nausea and anorexia after 7th course	45
VI	16	None	15+15	47	0	110	—	—
		20th	0	—	0	140	25 mg. only.	30
		25th	0	—	—	260	Nausea and vomiting after 34th course; returned to insulin 17-12	—
VII	60	None	10+5	41	0	100	—	—
		21st	0	—	0	160	25 mg. only	15
		30th	0	—	—	260	Urticaria	—
VIII	19	None	50+45+5	20	0	60-110	—	—
		3rd	30+25+5	—	0	60-140	Healing abscess	40
		None	40+25+5	32	0	50-80	—	—
		1st	25+15+5	—	0	60-160	Nausea and vomiting after 5th course	25
IX	15	None	14+12+4	32	0	50-110	—	—
		3rd	5+5+5	—	0	70-130	—	15
		7th	12+12	—	Trace	50-140	—	6
X	15	None	—	80	20	170-290	—	—
		1st	—	—	20	300	—	—
		2nd	—	—	4	140-260	—	—
		3rd	—	—	6	160-260	—	—
		4th	—	—	Trace	110-220	—	—
XI	6	None	20+10	30	12	330	—	—
		10+10	10+10	—	16	—	10 mg. daily	—
		10+10	12+4	—	6	—	—	—
		None	8+10+4	—	17	—	—	—
		15+15	0	—	38	330	15 mg. twice daily. Very ill; nausea and deep abdominal breathing	—
XII	49	None	8+8	40	0	120	—	—
		1st	8	—	Trace	200	25 mg. only	—
		2nd	8	—	Trace	200	25+25	—
		3rd	8	—	Trace	—	25+25	None
			10+8	—	0	140	—	—

A point of interest is that the weight increased by 2 lb. in the ten weeks of the synthalin treatment, and by 10 lb. in the next five weeks.

Case VII. A woman, aged 60, was given a diet of 40 grm. C., 66 grm. P., 107 grm. F., and required 10 + 5 units of insulin. Synthalin, 25 mg. in three-day courses, replaced both doses of insulin, and the blood-sugar remained within normal limits. She continued to feel well until after four months she developed a severe urticaria and the blood-sugar was 300 mg. per cent. This was thought to be due to the synthalin, and the drug was stopped. She now requires 10 + 5 units and the blood-sugar is not quite stabilized.

Case VIII. A woman, aged 19, who has been under treatment with insulin for four years. She is rather an unreliable patient, whose insulin requirements have risen to about 100 units a day as a result of various illnesses and dietetic indiscretions. She had been suffering from a small abscess following an insulin injection, and on a diet of 20 grm. C., 65 grm. P., and 100 grm. F. she required 50 + 45 + 5 units to keep the range of the blood-sugar within normal limits. After three courses of synthalin the insulin was reduced to 30 + 25 + 5 units. The decrease in the insulin occurred during the granulation of the sinus, and this may have been responsible for the decrease.

On another occasion when synthalin was given the dose of insulin was reduced from 40 + 25 + 5 units to 25 + 15 + 5 units. After three weeks the synthalin was stopped on account of nausea and vomiting, but the insulin was not increased, and within three days a severe state of ketosis with incipient coma developed, which necessitated large doses of insulin.

Synthalin a Failure.

Case IX. A boy who on a diet of 32 grm. C., 65 grm. P., 110 grm. F. required three injections of 14 + 12 + 4 units of insulin to keep the blood-sugar within normal limits. Synthalin, 50 mg., permitted a reduction to 5 + 5 + 5 units, but it was impossible to keep the blood-sugar normal with two doses of 12 units. A saving of only 6 units did not seem of sufficient value to continue the synthalin treatment.

Case X. A boy, aged 14, who had previously had insulin treatment was not having it at the time of these observations. He could take 50 grm. of carbohydrate with 65 grm. of protein and 110 grm. of fat in his diet without passing any sugar. On 80 grm. of carbohydrate, 17 to 20 grm. of sugar were present in the urine. The blood-sugar was then 170 to 290 mg. per cent. After four courses of synthalin the urine contained only a trace of sugar, and the blood-sugar was 110 to 220 mg. per cent. He had, however, pulmonary tuberculosis, which at this time showed signs of progression; he was therefore given a liberal allowance of food and treated with insulin.

Case XI. A small girl, aged 6, was having 27 grm. C., 60 grm. P., and 80 grm. F. The task of maintaining the blood-sugar normal with two doses of insulin was almost impossible, for a blood-sugar of 330 mg. per cent. might be converted into a severe hypoglycaemia some four hours after by 20 units of insulin, although the same dose might be quite well tolerated on the day before and subsequently. It was hoped that synthalin might be of great assistance in this type of case. Synthalin, 10 + 10 mg., was given for two days, and the insulin was reduced from 20 + 10 units to 10 + 10 units, and 12 + 4 units on the second day. The urine-sugar was somewhat lower at 6 grm. instead of 12 grm. On the third day no synthalin was given, and the urine-sugar, in spite of 22 units of insulin, rose to 17 grm. On the fourth day no insulin was given, and the

synthalin was raised to 15+15 mg. On this day she excreted 38 grm. of sugar and the next morning looked very ill. She had severe nausea and also vomiting, and the abdomen was moving deeply, as it does in coma. The blood-sugar was 330 mg. per cent. and the urine gave a very intense nitroprusside reaction. She recovered quickly with sugar and insulin. On a subsequent occasion synthalin was tried again for one course, but as it had no apparent effect it was discontinued.

Case XII. A man, aged 49, on a diet of 40 grm. C., 65 grm. P., and 117 grm. F., required 8+8 units to keep the blood-sugar within normal limits. One dose of 25 mg. of synthalin was given at night instead of 8 units, but failed to prevent glycosuria at night, and the blood-sugar on the first morning after the first course of synthalin was 200 mg. per cent. Synthalin, 25 + 25 mg., was then given for two more courses, and although the glycosuria was abolished at night, the morning blood-sugar on the next day was still 200 mg. per cent. As synthalin had so little effect it was not continued, and the blood-sugar was brought down to 140 mg. per cent. in the morning by 10+8 units of insulin.

Discussion.

The observations which we have made on these twelve patients under carefully controlled conditions show that in eight out of the twelve, synthalin caused a very definite and apparently beneficial change in their carbohydrate metabolism. In one instance a dose of 50 mg. of synthalin was able to replace 40–45 units of insulin, without the blood-sugar exceeding the normal limit. In four cases the synthalin had an action corresponding to 15 units of insulin or less, or even no observable action at all.

These results are not nearly so good as those reported by the early workers (5, 12, 13, 14, 15, 16), but they are very much better than some reported (18, 19). The explanation of this wide difference of opinion is not obvious, since the experiments were made under conditions which seemed as good as could possibly be obtained for a fair test.

A possible explanation may lie in the reaction of the individual patients. Insulin is a natural secretion and is always effective in lowering the blood-sugar, provided that enough is given: true, 'enough' may mean 100 or more units instead of the 10–20 which are usually sufficient. Synthalin is a foreign chemical and has no action on sugar in the test-tube; its mode of action is still obscure. It must act on carbohydrate metabolism through an action on the body in modifying cellular activity; possibly an isolated phenomenon, but possibly part of the more general toxic action which it always shows when given in larger doses.

If the action of synthalin on carbohydrate metabolism has no relation to its toxic action, a close parallel may be found in another elaborate synthetic group, the salvarsan group. Salvarsan does not kill spirochaetes by itself, but is able to produce an active spirochaetocidal action from the body in most cases, yet it sometimes fails because of something apparently lacking in the response of the individual. The jaundice, dermatitis, and other undesirable effects of salvarsan in a few unfortunate individuals are comparable to the nausea and jaundice of

synthalin, and it may be observed that the early members of the salvarsan series showed undesirable reactions much more frequently than those to which we are now accustomed. Idiosyncrasies of this kind are well known. Thus, patients with an inborn 'error', e.g. alkaptonuria or cystinuria, are unable to use homogentisic acid or cystine. Similarly, patients who appear quite normal in other respects develop abnormal signs with bromides, iodides, or salicylates.

On the other hand, the action of synthalin on carbohydrate metabolism may be but a part of its general toxic action. Its beneficial action may be due to depression of the liver's power to deaminize amino acids, since this activity is increased in the diabetic state. This may be regarded as due to a slight degree of poisoning of the liver, the more severe degrees of which are shown by the nausea, vomiting, pain, and jaundice of synthalin poisoning. The fact that a third of our patients were unable to make effective use of the drug limits its use in general practice.

The toxic properties of synthalin are a very serious disadvantage, for although they are less severe than those of guanidine itself they are sufficiently unpleasant to make patients refuse to run the risk again. They occurred in five out of our twelve patients, four of whom had shown that they could use synthalin to spare insulin, and in two of these the drug had been used for some months.

There is some evidence that the toxic action is on the liver, for animals which die with a hypoglycaemia that has not been relieved by sugar have no glycogen in the liver. This is confirmed by the observation of Dale (20) that adrenalin, which is known to act by turning glycogen out of the liver, fails to raise the blood-sugar in these cases. Adler (11) reported one case of jaundice which ended fatally, and also observed one case in which the patient recovered. It was for this reason that he has used dehydrocholic acid 3 grains with each dose of synthalin. Decholin causes an increase in the flow of bile, and may perhaps aid in the excretion of synthalin from the liver. Adler claims that with decholin he can use bigger doses of synthalin without causing any symptoms. We did not have any decholin for the early cases, and in the patients (Cases VII and VIII) the symptoms began after they had left hospital, and under the circumstances it seemed wiser from the patient's point of view to revert to the use of insulin. We incline to the view that decholin should be used from the outset of treatment, since the toxic symptoms are so unpleasant that once experienced few patients want to run the risk again.

The question of the dose of synthalin is very important for avoiding toxic symptoms. Frank recommended that it should not be given to children, and Priesel and Wagner (24) failed altogether in its use. However, Hirsch-Kauffmann and Heimann-Trosien (25), working in the Children's Hospital at Breslau, obtained quite good results, but pointed out that the dose must be a very small one. The dose which caused such severe symptoms in Case XI of this series would appear to have been much too large. If this work is correct, the right way to use synthalin would be to start with small doses and very gradually increase them, using decholin all the time.

Another point must be considered, because we do not yet know what is the fate of the sugar which disappears. It is not found in the liver nor in the muscles as glycogen, and the lactic acid which is formed disappears again. There is no evidence at present that the sugar which disappears serves any useful purpose.

Synthalin may only act by destroying sugar after it has been absorbed into the blood and thus resemble the action of yeast, which can destroy the sugar while it is in the stomach and thus prevent a rise in the blood-sugar.

Against this point is the observation on Case VIII. The patient suffered from a severe ketosis and air hunger three days after the synthalin had been stopped, because of some slight toxic symptoms. This suggests that the sugar which was disappearing under the influence of synthalin was at least acting in an anti-ketogenic capacity.

There is no good evidence that the patients are really better for having it. One man, Case III, gained 14 lb. in weight, but then he was having 18 units of insulin as well. The woman, Case IV, did not gain any weight—being already over-weight—and she had no insulin. The boy, Case VI, gained 2 lb. in ten weeks, and 10 lb. in five weeks after restarting insulin.

The important question in connexion with synthalin is: Has it any place in the treatment of patients with diabetes mellitus? The evidence makes it quite certain that it does not act in the same way as insulin, which is the natural secretion. Therefore, those patients who need insulin will always be well advised if they will use it. If patients, however, object to the inconvenience of a daily injection, or have a prejudice against having anything injected, synthalin is worthy of a trial under careful conditions.

The initial doses should be small and only given for two or three days at a time, and perhaps combined with decholin so as to avoid any of the toxic symptoms.

Conclusions.

Synthalin does have some effect on the glycaemia and glycosuria of diabetic patients, but in this series only acted in eight out of twelve cases.

The toxic symptoms are serious, and should be avoided if possible by smaller dosage and careful spacing of the dose.

Synthalin should only be used if the patient will not try insulin.

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SPRUE

AN ANALYTICAL STUDY OF 150 CASES[1]

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I KNOW of no better definition for sprue than that given by Sir Patrick Manson, in his *Tropical Diseases*, sixth edition, 1917, page 549: 'By the term "sprue" is understood a peculiar and very dangerous form of chronic catarrhal inflammation of the whole or part of the alimentary canal, generally associated with disturbance of the chologenic function of the liver and, probably, of the functions of the other glandular organs subserving digestion. Although a disease of warm climates, it may develop for the first time in temperate climates; only, however, in individuals who have previously resided in the tropics or sub-tropics.'

From the aetiological standpoint the causative agent of the disease is still unknown. We know, however, of many predisposing factors, such as prolonged residence in the endemic area, diseases of the alimentary canal, such as hill diarrhoea and dysentery; in short, any debilitating disease—syphilis included—may bring it out. Lately I have seen an interesting series of cases of young men who acquired the disease when serving in India in the War, and who had only been in the endemic area one or two years. The disease occurs in natives, but rarely; I have seen three such cases in Indians, here in England. As regards organisms, monilias have been described, but as far as one can judge these are not the real cause of the disease and only occur as secondary contaminators. The anatomical lesions found at autopsy are suggestive, and evidence is accumulating to show that the disease is infective. Others, however, consider that a gastro-intestinal toxin may best explain the real cause of the disease. Periods of latency are met with, the disease not breaking out until the patient has been months or even years at home and away from the endemic area. Both sexes are equally affected.

Geographically, certain parts of the world are much more prone to the disease than others. It is especially common in the East—China, Cochin China, Manila, Java, Sumatra, Singapore, the Federated Malay States, Burma, and India, especially in Bombay. It has been met with in Africa, but is rare there. In the West Indies it is of frequent occurrence in Porto Rico, and also has been noted in some of the other islands. I have also had cases from British Guiana, North Queensland, and Mexico.

[1] Received May 10, 1928.

The chief symptoms of sprue may be tabulated as follows:

1. Loss of energy.
2. Loss of weight.
3. Dyspeptic distension of abdomen.
4. Morning diarrhoea. White frothy stools.
5. Sore mouth and tongue.
6. Anaemia, especially in the later stages.

Having made these few preliminary remarks one may now pass on to an analysis of the 150 cases which form the basis of this study. These were all treated in London during the last twenty years. They may best be analysed under the following heads: I. Age. II. Sex. III. Duration of illness. IV. Place of infection. V. Previous illnesses. VI. Tongue symptoms. VII. Mouth symptoms. VIII. Diarrhoea. IX. Flatulence and abdominal symptoms. X. Loss of weight. XI. Liver dullness. XII. Blood condition. XIII. Other symptoms. XIV. Treatment. XV. Approximate time under treatment. XVI. Results. XVII. Remarks.

I. Age.

The youngest case seen was 21, the oldest 75. Dividing up the ages into periods, the greatest number of cases occur in the middle period of life, broadly from 30 to 60. The following table illustrates this:

TABLE I.

Year periods.

20-30.	31-40.	41-50.	51-60.	61-70.	Over 70.
26	39	41	32	10	2

II. Sex.

Many more males than females were seen, but I do not think that this means that the female is less liable than the male. The most likely explanation is that more males than females go abroad and consequently more of the former will be seen than the latter. In the series there were 112 males and 38 females.

III. Duration of Illness.

This was computed in 113 of the cases and deals with the time that the patient had had symptoms of the disease before seeing myself. The majority had only noticed signs for some months, 4 to 8 say, and, on a diagnosis being made, came home to England. Others, however, often not diagnosed at first, did not seek aid until a year or even more had elapsed from the onset of their symptoms. The following table shows this:

TABLE II.

Under 1 yr.	1.	2.	3.	4.	5.	6.	7.	8.	9 yrs.
32	30	18	14	3	6	3	3	2	2

IV. *Place of Infection.*

The great majority of cases are from India, China coming second. As regards India, if the patient had only lived in Bombay and evidently acquired the disease there, the case is entered as Bombay, otherwise under India generally. East Africa, Queensland, Mexico, and Fiji are all represented. The following table gives the details:

TABLE III.

China	27	Assam	2	British Guiana	2
Japan	1	India	68	Mexico	1
Hong Kong	4	Ceylon	10	Fiji	1
Singapore	2	Bombay	7	North Queensland (Australia)	2
Manila	1	Mesopotamia	1		
Federated Malay States	8	East Africa	2		
Penang	2	West Indies	1		150
Burma	7	Barbados	1		

V. *Previous Illnesses.*

In 91 of the 150 cases, 61 per cent., a history of some debilitating illness was obtained. It is true that in many of the cases this had been acquired some years before the symptoms of sprue developed, but in others a definite relationship between the two could be traced. There does seem to be a connexion between the different forms of dysentery, hill diarrhoea, and possibly enteric, as predisposing factors. In two cases typical sprue developed on the top of amoebic dysentery, the stools definitely changing from those of dysentery to those of sprue. Syphilis also coexisted in a good number of the cases, and there is a definite condition which appears in that disease and closely resembles real sprue. This pseudo-sprue yields to anti-syphilitic remedies. I have had six such cases, but they have not been included in the 150 cases analysed because they are not sprue. The following table summarizes the conclusions:

TABLE IV.

Amoebic dysentery	15	Enteric	5	Dengue	4
Dysentery, including bacillary and other forms	17	Malaria	14	Gastric influenza	1
Dysentery and enteric	3	Diarrhoea	3	Ankylostomiasis	1
Dysentery and malaria	10	Hill diarrhoea	6	Cholera	1
		Syphilis	10		
		Sandfly fever	1		91

VI. *Tongue Symptoms.*

The inflammatory condition—the pathological syndrome of the disease—very frequently attacks the tongue, giving rise to a clinical condition of glossitis or, as it is popularly known, 'sore tongue'. When this occurs the organ is red, inflamed, congested, and very painful, the epithelium is destroyed, and often minute vesicles or little ulcers are seen along its margins. Alcohol, condiments, &c., cannot be taken owing to the intense pain they produce, and the irritation produced by the lesions may cause a profuse salivation.

On recovery from the acute or subacute manifestations the epithelium is seen to be denuded, leaving the tongue smooth and bare. It is now an ordinary

colour and no longer painful. Exacerbations are, however, prone to occur with a renewal of the inflammatory changes. Finally, when complete recovery takes place, a new epithelium is developed and the tongue becomes covered again. In cases complicated with syphilis transverse fissuring is often seen, and patches of leucoplakia may appear, giving the well-known silvery tongue. This often gives the clue to the mixed infection.

Of the 150 cases, 101 had tongue lesions when seen, the symptoms varying in intensity and appearance with the state of the disease. The smooth bald tongue was common in the chronic advanced cases.

In most of the others, with the exception of 14, there had been a history of sore tongue or mouth at some period of the illness. The 14 (9 per cent.) had never suffered from tongue or mouth lesions at any time up to the time of being seen.

VII. *Mouth Symptoms.*

These are similar to those of the tongue, the principal lesions being small superficial ulcers in the buccal mucosa. Patches of inflammation and congestion are also seen, these spreading back to the pharynx and even down to the oesophagus. Of the 150 cases, 44 were noted as having mouth symptoms at the time of the examination. One cannot, however, draw any fast distinction between tongue and mouth lesions, most patients having one or the other at one period of the disease, and often both together, as the table shows.

In the series oesophageal symptoms, as evidenced by pain in swallowing, soreness, and the feeling of a raw surface down the gullet, were specially noted in 4 cases.

TABLE V.

Tongue Symptoms.	Mouth Symptoms.	Oesophageal Symptoms.	Negative.
101	44	4	14

The teeth are invariably bad in sprue, pyorrhoea and root sepsis being very common. The part this chronic septic absorption plays in keeping up, or even aggravating, the symptoms is very important.

VIII. *Diarrhoea.*

The diarrhoea of sprue is peculiar. One of the earliest, if not the earliest, symptoms of the disease is that it usually comes on in the early hours of the morning—from 3 or 4 a.m. onwards—the patient having to get up once, twice, thrice, or even oftener before breakfast. After this the rest of the day is quiet with no trouble, but next morning a repetition of the same thing takes place. After this has lasted for some time the characters of the stools change: they become very offensive, frothy, and of a white colour, the usual brown pigment disappearing.

As time goes on, and especially if the patient is not treated, the diarrhoea becomes excessive and occurs throughout the day as well as in the mornings.

Twelve to fifteen stools a day may be passed, and rapid wasting now takes place. On strict diet and treatment the diarrhoea may be checked and then the stools become solid again, but without any colour in them.

The absence of colouring is interesting. Bile is still secreted, but the colouring matter, the bilirubin, is said to be changed in the intestine into a colourless substance known as leucobilin or leuco-urobilin. This is synonymous with urobilinogen. It is interesting that one of the signs of a return to normal is the gradual appearance of colouring matter in the stools again.

A clinical analysis of sprue stools shows great excess of fat, with the fatty acids in excess of the neutral fat, this indicating that a certain amount of splitting is taking place and that there is no pancreatic insufficiency in the sense of absence of lipase, but rather the reverse. Apparently, however, owing to lacteal destruction this is not absorbed, and is passed in the faeces unchanged.

The amount of fat varies, but may be as high as 70 to 80 per cent., with the fatty acids in the proportion of 5 to 1 of neutral fat, or even higher up to 10 to 1. In a recent case of sprue in a native (not included in this series) the readings were:

Total faecal fat	67·86	per cent.
Combined fatty acids	18·75	„ „
Free fatty acids	42·71	„ „
Neutral fat	6·4	„ „
	67·86	„ „

This helps one in diagnosing sprue from diseases of the pancreas, where the neutral fat is greatly in excess of the fatty acids, indicating a failure of the lipase ferment.

No parasitic helminths or protozoa are present, unless a mixed infection coexists. The stools in the later stages of the disease tend to become very bulky, and food, if not of a proper nature, is passed undigested. The pathology of the disease explains the faulty assimilation that is taking place, for a large part of the intestine is out of action and cannot therefore absorb nutriment properly. Though careful and prolonged bacteriological researches have been conducted on the faeces in sprue, no specific micro-organism has been isolated. The possibility of a gastro-intestinal toxin as the cause of the disease cannot therefore be ignored.

Out of the 150 cases a history of diarrhoea, at some time or other, was obtained in 141. The majority actually had this when seen; others were in the remission stage, better for the time being, only to relapse again later; while others were convalescent and practically cured. In nine cases there was no definite history of diarrhoea, the tongue and mouth lesions, the wasting and blood changes, giving the clue to the diagnosis.

TABLE VI.

With Diarrhoea.	Without Diarrhoea.
141	9

IX. Flatulence and Abdominal Symptoms.

Flatulence with dyspepsia and gastric symptoms is one of the cardinal signs of real sprue. Due no doubt to the loss of tone in the intestine and the presence of many gas-forming organisms, this flatulence distends the abdomen until it becomes like a drum. It is very distressing and difficult to cure. In its absence the walls of the abdomen are seen to be soft and flabby, with little or no tone left in the muscles and with the panniculus atrophied away. This sprue abdomen is very characteristic. In the 150 cases there were 75 (50 per cent.) noted as having flatulence at the time of their examination. In fifteen definite abdominal pain was complained of, in four a general sense of discomfort only, and in one cramps in the abdominal wall.

TABLE VII.

Flatulence.	Abdominal Pain.	Abdominal Discomfort.	Cramps in Abdomen.
75	15	4	1

X. *Loss of Weight.*

This may be taken to be a constant feature in the disease. No disease, with perhaps the exception of cancer, produces such a rapid and extensive loss of weight. Here again the pathology explains this. Most of the absorbing surface of the small bowel is thrown out of action and the patient is being starved, though taking plenty of food. Finally, sufferers from sprue may become emaciated skeletons, with their ribs and other bones showing through the dry, atrophic skin with which they are covered. It is no uncommon thing for a man of 12 stone, say, to lose a quarter of his weight or more. Small people, especially women, may fall well under 6 stone. Loss of weight is constant and occurred in all the 150 cases. It was specially investigated in 100 of these, losses of weight such as $4\frac{1}{2}$ stone, 4 stone, 3 stone, and 2 stone being common.

XI. *Liver Dullness.*

The liver is shrunken in sprue and the dullness to percussion is consequently diminished. This may be due to a special change in the liver itself, or only part of the general atrophy. Sokhey, Gokhall, Malandkar, and Billimoria (*Indian Journal Med. Research*, xv, 1928, pp. 553–61) have studied thirteen cases to see if modern functional tests would throw any light on the efficiency of the liver in sprue. Their conclusions show 'that in sprue the liver is not affected to such an extent as to show impairment by liver function tests'. The following tests were employed:

1. Levulose tolerance test.
2. Van den Bergh reaction.
3 Nitrogen partition of blood.
4. Bromsulphalein dye test of Rosenthal and White (1925).

As has been said previously, bile is still secreted into the intestine. In the analysis, only 67 cases have been specially recorded as to the condition of the liver, but certainly, if looked for carefully, this shrinkage would be found to be commoner than the figures below indicate. Even then, 64 (42·2 per cent.) showed marked diminution of this organ.

TABLE VIII.

Liver Dullness decreased.	Liver Dullness not decreased.	Liver Dullness increased.	Unrecorded.
64	2	1	83

XII. *Blood Condition.*

In the early stages of sprue there may be no anaemia, but later, especially in the chronic cases, anaemia appears. In a certain type of case, which may be described as the 'haemolytic type', a progressive loss of red blood corpuscles takes place, and a picture closely resembling pernicious or Addisonian anaemia develops. Many of these cases die with blood counts down to half a million reds per c.mm. or under. Though this is so, it does not mean that sprue is the same disease as pernicious anaemia, but it is possible that it is produced by similar causes, such as gastro-intestinal or other toxins. In the early and mild cases with little anaemia, the cure of the sprue cures the anaemia, and as long as the disease is cured or in abeyance the anaemia does not return. In the haemolytic types, however, even with apparent cure or at least amelioration of the symptoms, the anaemia may continue independently, and it is this class of case that resembles pernicious anaemia. The blood was investigated and counted in 114 of the cases; 7 cases were reported to have no anaemia, while 5 were reported anaemic but with no details of blood counts.

TABLE IX.

Under 1,000,000.	1 to 2 Million.	2 to 3 Million.	3 to 4 Million.	4 to 5 Million.	5,000,000 or over.	
1	7	14	43	45	4	= 114 cases

This table shows that many of the cases had counts between 4 and 5 million reds, indicating little disturbance, while the next highest figure comes in the category 3 to 4 million. The haemolytic type in this series of 114 cases numbers 8, and there are 14 borderland cases. The lowest count obtained was 840,000 per. c.mm., the highest 6,200,000. Outside this series, however, I have seen cases at 645,000 per c.mm. and 780,000 per c.mm.

The leucocytes in sprue are about normal; where the anaemia is severe a leucopoenia may occur, while in a few cases a leucocytosis may be met with, indicating some other infection. The following table gives the leucocyte counts in the 114 cases:

TABLE X.

1–2,000	3	5–6,000	21	9–10,000	1
2–3,000	1	6–7,000	44	10–11,000	3
3–4,000	5	7–8,000	20	over 11,000	5
4–5,000	9	8–9,000	2		
				Total	114

In one case the leucocytes reached 18,000, the highest count recorded. The reason of this was not clear, no definite complication being noted.

The haemoglobin, as a general rule, is reduced in proportion to the reds, giving a colour index of 1. Nucleated reds and abnormal corpuscles are seen in the severe grades of anaemia in the haemolytic types, and there is a tendency here also for the haemoglobin to rise, giving a colour index greater than 1·0.

XIII. *Other Symptoms.*

Symptoms other than those described as the classical ones of the disease were encountered in the series, some due to the disease itself, while others may have had little or no connexion with it.

Of these, the following may be mentioned: Cachexia with pigmentation of face and skin; mental changes indicated by irritability of temper, fretful disposition, &c.; oedema of ankles and feet; pyrexia; dry skin; cramps in muscles and stomach; sudden vomiting (3 cases); appendicitis; haemorrhoids (common); petechial haemorrhages; stoppage of menstruation; auricular fibrillation; syncopal attacks. Strangely enough, though tetany is described as a common symptom of sprue in all text-books, it was not seen at all in the 150 cases analysed.

XIV. *Treatment.*

There is hardly any disease in which treatment is so important as in sprue, and unless the patient makes up his mind to undergo the drastic measures one has to adopt, there is no chance of curing the disease. Absolute rest in bed is the first essential, and no movements of any sort should be allowed for six weeks to two months. The patient must lie on his back and not get out of bed even to go to the closet. The bed-pan and bottle must be used. Diet is the second essential, and if one bears in mind the pathological lesions present in the intestines, then it will be apparent that, to begin with, the most easily digested and easily assimilated food must be employed, and in this respect nothing comes up to milk. The routine I adopt in sprue is as follows, and this was followed out more or less in all the 150 cases of the series.

It is best to commence with a comparatively small amount of milk until the diarrhoea and other acute symptoms disappear. Three pints of milk in the twenty-four hours will be found to be enough. The feeds should be given every two hours with the exception of 2 and 4 a.m., this making ten feeds a day, e.g. 6 oz. of milk per feed. On this alone the symptoms very quickly—almost at once in most cases—begin to improve; the diarrhoea ceases and the faeces tend to become solid. The weight, however, still goes on falling, as three pints of milk a day is not sufficient to maintain an adult's weight. Whenever signs of improvement appear, the milk should be gradually increased, and when amounts up to five pints are being taken and digested, the weight starts to go up. Progress as a rule now goes on without any untoward incident, and I gradually work up to a

maximum of seven pints in the twenty-four hours. In small males and in females six pints may be all that can be digested. The total time devoted to the strict milk régime has generally been four to six weeks. If at the end of that time everything is satisfactory, then the gradual introduction of carbohydrates is begun. Sago or arrowroot may now be given. Later, eggs are started, first beaten up with the milk, then lightly boiled, then rusks and toast. By this time two months will have passed, and, if all is well, in the third month pounded fish, fruit in the form of bananas, pounded chicken, potatoes and spinach as a vegetable, may be given. A simple diet of this nature is continued as long as the patient is in hospital or in a nursing home, and then when leaving one should lay down a simple dietary which must be continued for the next six months at least. No irritating foods must be taken, absolutely no alcohol is allowed, and great caution must be observed against damp, cold, chills, and over-exertion.

Treatment has a marked effect on the blood. In early cases, as has been stated, there may be little or no anaemia. In later cases anaemia develops, but on drastic treatment being adopted this at once improves and the blood gradually returns to normal. In the haemolytic types it is much more difficult to get improvement, however, and if the anaemia is in any way severe, transfusion of blood is undoubtedly the best method to adopt to cure this. This is well shown in the series of cases published by Dr. Cooke and myself (*Lancet*, 1927, 11, p. 960). In these a large quantity of blood, 500 c.cm. or over, was used, but more recently we have been trying small injections of whole blood, 10 c.cm. only, and in two cases this has seemed to supply the stimulus necessary to start the blood regenerating again. It must be borne in mind that sprue is one of the diseases in which auto-agglutination of the blood takes place, and special precautions have to be taken in transfusing to prevent bad effects appearing. It would seem that undue cooling of the blood is specially dangerous, and this must be guarded against. The grouping must also be carefully gone into.

Drugs may be employed, and of these arsenic comes first. It is best given by intramuscular injections, and the addition of iron is not prejudicial, but rather the reverse. Squire's arsenate of iron in doses of 7 minims every alternate day, or Fraise's preparation, can be employed. Iron is badly tolerated by the mouth in cases of sprue, but some cases can take arsenic in the form of liquor arsenicalis (Fowler's solution) by the mouth, often with great benefit. The dose, small to begin with, should be gradually increased up to 7 or 8 minims three times daily, till signs of intoxication appear. After this a rest is given, this being followed up by another course, and so on. One of the chief signs of improvement, indicating that things are going well, is the gradual steady increase of the red cells. After the blood has returned to normal it should, however, be tested at intervals of two months or so, to make certain that the improvement is maintained.

XV. *Approximate Time under Treatment.*

The time under treatment for sprue varies considerably. It may best be divided into periods, viz. (1) that in which the patient is in hospital or in the

nursing home, and (2) that in which he goes out as a convalescent. A table has been constructed dealing with (1), and figures are available for 140 of the cases. From this it will be seen that the bulk of the patients have to be ten to twelve weeks—most of the time in bed—under strict control.

TABLE XI.

Duration in Hospital or Nursing Home, in Weeks.

Weeks	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	21.	23.	24.	25.	28.	29.	
	5	6	2	5	7	3	8	8	20	10	12	7	4	3	8	3	5	11	4	3	2	1	2	1	= 140 cases

Even after this strict control and dieting the patient is not cured, and he should be warned of this when he goes out, as this is the most crucial time in the whole treatment. Though doing well in hospital, many quickly relapse on going out, and this is due, no doubt, to damp and cold in winter, unsuitable diet, eating things outside the dietary, drinking alcohol, &c. The sprue case should still continue his simple, light diet for a year after all symptoms of the disease have disappeared. If possible, he should not return to the endemic area where he acquired the disease.

XVI. *Results.*

It is difficult to estimate the end results in most cases, as many patients drift away and are never heard of again. The axiom stands good, that young cases under 30 will, if they stay in this country, recover completely. Older cases may, but age plays a very important part in the prognosis of sprue, and the older the patient the more difficult it is for complete recuperation to take place. Again, chronic cases, where the symptoms have lasted for years, are notoriously difficult to cure completely. We may patch them up, so to speak, but any indiscretion or want of care is apt to be followed by a recrudescence of the symptoms. It is possible that with the more general introduction of blood transfusion, as described above, better end results will be obtained, but even now, with strict régime and sensible patients, we get quite good results. The chronic long-standing cases are the difficult ones. Many of these, as has just been said, drift away into other hands and eventually die either of the sprue or of some superimposed infection. There is no doubt that the ultimate effects of sprue in the end are responsible for many deaths. The disease must be looked upon then as one of the serious tropical maladies, not quite, perhaps, in the same category as dysentery, malaria, plague, and cholera for death-rate statistics, but nevertheless approaching them if the cases are followed up to the end. As a cause for invaliding and cessation of tropical service, sprue is in the first rank.

Out of the 150 cases, a good number of results have been obtained, but in most of them no real end ones, because of the difficulties before mentioned. Of a small series of young men (included in the 150) who acquired sprue when on military service in India for a short period during the Great War, all were

definitely cured. In addition to these, who numbered eight, I know of fourteen others who have been absolutely cured and have never shown any trace of the disease again. Satisfactory results, by that meaning in all probability a complete cure, are fairly numerous, as the table shows. 'Improved' means that the disease was still present and would certainly break out again, especially if indiscretions of diet were indulged in. In the category of not improved come those who refused to go on with the treatment, or who, even on treatment, did not respond. Most of these, if it had been possible to follow them up, would sooner or later have died. The table gives the summary of the figures available.

TABLE XII.

Cured.	Satisfactory.	Improved.	No Improvement.	Died.	Unaccounted.	Total.
22	60	22	16	10	20	150 cases

The ages of these have been worked out. They show again that age plays an important part in the prognosis of the disease, the younger the patient the better being his chance of complete recovery. On the other hand, in the twenty-two definitely cured cases, five at least are over 50, and one close on 70. Most of those who did badly were well over 50 and in addition were cases who had suffered from the disease for years. Six of the ten deaths were severe cases of the haemolytic type, one had purpuric haemorrhages, one died of pneumonia, one of general wasting, and of one there is no record.

XVII. *Remarks.*

From what has gone before it will be seen that sprue is a very important tropical disease, and an intestinal toxin, probably, best explains its symptomatology. Little has been said in the text about specific drugs. Yellow santonin had a vogue for a time, but personally I could never see any special results following its use. I have tried parathyroid and calcium lactate in a few cases not included in this series. In the last years, for the purposes of comparison, Dr. Manson-Bahr has used this method of treatment and I have not. The results obtained have been equally good in those who did not have the drug and in those who did, so that one cannot say it has been of special benefit. The use of strawberries is remarkable in certain cases. It must be borne in mind, however, that some cases do not tolerate the berries, while in others they have no effect at all, and that it is only in a small group that occasionally wonderful results are met with. They should certainly always be given a trial when available. Lime would seem to be of value when the diarrhoea is present, and it may be given in the form of Batavia powder in drachm doses three times a day. This has been used in many of the cases analysed above. The so-called meat treatment has never given satisfactory results in my hands and is in every way inferior to the milk treatment. As regards going back to a tropical climate, we must consider each case on its own merits. It is better that such cases should not, but in certain instances necessity has compelled a return and no ill effects have arisen.

Prophylaxis must necessarily remain in abeyance until we discover the exact aetiology of the disease. The cause, however, must be a common one, in view of the large number of people who acquire the malady. Moderation in diet and alcohol are advisable, but even with this, for example in the case of missionaries, sprue may be acquired. As has been shown in the earlier part of the analysis, certain parts of the world are much more subject to the infection than others.

My best thanks are due to Dr. R. M. Morris, Dr. S. M. Anderson, and Dr. W. E. Cooke, of the Hospital for Tropical Diseases, Endsleigh Gardens, and to many others, for their care in taking the notes of the cases and for considerable help in drawing up the analysis.

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-FIRST ANNUAL GENERAL MEETING

The Twenty-first Annual General Meeting was held at Belfast on Friday and Saturday, June 3 and 4, 1927. The proceedings began at 10 a.m. The morning sessions were held in the Physics Department, Queen's University, and the afternoon sessions in the Royal Victoria Hospital.

The President, Sir David Drummond, was in the Chair.

The minutes of the last Annual Meeting, having been published in the *Quarterly Journal of Medicine,* were taken as read and confirmed.

Election of Officers.

President. Professor James Lindsay was elected President for 1927–8. On his election he took the Chair and expressed the thanks of the Association to the retiring President, Sir David Drummond, for his services during the past year.

Honorary Member. Sir David Drummond was elected an Honorary Member.

Election of Officers, members of the Executive Committee, and new members followed.

President. Professor J. A. Lindsay.

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England:

Dr. J. W. McNee.
Dr. J. C. Matthews.
Professor F. Craven Moore.
Dr. F. J. Nattrass.
Dr. J. A. Ryle.
Dr. R. A. Veale.

Members for Scotland:

Dr. L. Findlay.
Professor A. Patrick.
Dr. W. T. Ritchie.

Members for Ireland:

Dr. S. B. Boyd Campbell.
Dr. J. S. Morrow.
Dr. W. A. Winter.

ASSOCIATION OF PHYSICIANS

New Members.

Lancelot Stephen Topham BURRELL, M.D., Assist. Phys., West London Hospital.

Archibald Edmund CLARK-KENNEDY, M.D., Assistant Director of the Medical Unit, London Hospital.

Terence EAST, M.D., Medical Tutor and Lecturer, King's College Hospital.

John GRACIE, M.B., Physician, Western Infirmary, Glasgow.

Rowland HILL, M.D., Assist. Phys., Belfast Hospital for Sick Children.

Charles George LAMBIE, M.B., Assist. Phys., Royal Infirmary, Edinburgh.

William McLORINAN, L.R.C.P.I., Senior Physician, Mater Infirmorum Hospital, Belfast.

Robert James ROWLETTE, M.D., Physician, Mercer's Hospital, Dublin.

Lewis Hay Frederick THATCHER, M.D., Physician, Royal Hospital for Sick Children, Edinburgh.

Arthur Peregrine THOMSON, M.D., Assist. Phys., General Hospital, Birmingham.

John Forbes WARD, M.D., Assist. Phys., Manchester Children's Hospital.

Charles McMoran WILSON, M.D., Physician, St. Mary's Hospital.

Presentation of Treasurer's Accounts. Dr. Morley Fletcher presented the Annual Report, which was adopted. This showed a balance of £185.

Annual General Meeting in 1928. A letter was read from Professor John Hay inviting the Association to meet in Liverpool in 1928. The invitation was cordially accepted.

Medical Science and Abstracts. A letter was read from Sir Walter Fletcher stating that the Medical Research Council reported that they were unable to renew the publication as there appeared to be no demand among those engaged in research.

Quarterly Journal of Medicine. It was announced that a letter had been received from Dr. A. G. Gibson, the Secretary to the Editors, stating that owing to the large amount of valuable material now being received, the Editors desired to increase the size of the Journal. This would necessitate an increased subscription from the Association. The matter was referred to the Executive Committee with power to co-opt Sir William Hale-White, Sir Archibald Garrod, and Dr. Gibson, the Committee to report to the Association before the end of the meeting.

SCIENTIFIC BUSINESS.

Friday Morning, June 3.

1. Dr. A. Dingwall Fordyce on 'Mental Efficiency and Rheumatic Infections'. He had found that of feeble-minded children 10 per cent. had organic heart disease, 5 per cent. being congenital, and 5 per cent. rheumatic. In those definitely rheumatic, the general intelligence is usually approximately normal, measured by Burt's revision of Binet-Simon tests, even when scholastic intelligence is markedly impaired.

These children should therefore school with mentally normal children, but with special individual attention.

2. Dr. D. K. Adams gave a communication on certain points concerning disseminated sclerosis. With regard to spirochaetes, there was no scientific proof either for or against their relations to the disease. The importance of the colloidal gold reaction was urged. Retrobulbar neuritis needed investigation.

Dr. Kinnier Wilson considered that the histological changes differed from those of spirochaetal diseases.

Dr. Tidy and Professor Kauffmann suggested that the disease might be due to intestinal toxins, the aromatic sulphates in the urine showing large variations.

Dr. Cassidy and Dr. Patterson also spoke.

Dr. Adams, in reply, stated that the colloidal gold reaction gave a positive result in a high percentage of cases. He considered that salvarsan treatment gave good results.

3. Dr. Gordon Holmes on 'Some Nervous Symptoms in Leukaemia'. He described the case of a boy who rapidly developed spastic paralysis with anaesthesia to the level of the xiphoid. The condition varied rapidly, disappearing and returning. Later he developed enlarged glands and spleen, and haemorrhages, and was found to have the blood changes of myeloid leukaemia. At autopsy, three and a half months later, two firm masses were found in the cord at the level of the second dorsal and seventh dorsal, and the lumbar roots were infiltrated.

Dr. L. Ball and Dr. Carslaw mentioned similar cases.

Lord Dawson referred to the cases of Hodgkin's disease with paralysis which were described at the meeting last year.

Dr. Tidy and Dr. Thursfield also spoke.

Dr. Gordon Holmes, in reply, did not believe that pressure on the circulation could produce the transient paralysis.

4. Dr. Kinnier Wilson on 'Narcolepsy and some other Disorders of Sleep'. Narcolepsy is characterized by the combination of attacks of sleep occurring during daytime, with attacks of loss of tone in the muscles. The sleep is always light and of short duration, not exceeding half an hour. An attack of loss of muscular tone will follow such stimuli as laughing or noise or an emotion.

The condition has some relations with epilepsy. Some cases are post-encephalitic. Others had followed head injuries.

In an interesting discussion which followed, similar cases were described by Professor Lindsay, Dr. Nattrass, Dr. Gordon Holmes, Dr. Ryle, and Dr. A. G. Gibson.

Dr. Kinnier Wilson replied briefly.

5. Professor W. W. D. Thomson described 'A Case of Intracranial Chondroma'. There was proptosis of the right eyeball, constant pain referred to right eyebrow, and choked disks. X-ray examination showed areas of calcification in the right frontal lobe and erosion of right superior orbital margin. At autopsy a pearly white, nodular tumour was found embedded in the right frontal lobe. It fell out on removing the brain, and had apparently been attached to the meninges covering the right orbital plate by a fine fibrous pedicle. It was about the size of a tangerine orange and was composed of pure hyaline cartilage.

2–3 p.m.

1. Demonstration of clinical cases (51) at the Royal Victoria Hospital.

2. Demonstration of neurological preparations by Dr. R. H. Hunter.

3. Exhibition of prints and books lent by the Linen Hall Library and the Municipal Art Gallery, Belfast.

Friday Afternoon. 3 p.m.

The Secretary reported that the Executive Committee had met to consider matters referred to it as the result of Dr. Gibson's letter. The substance of the proceedings was laid before the Association. The principal points were: (1) that a large amount of material was awaiting publication and could only be dealt with by enlarging the Journal; (2) that the Clarendon Press could not publish more than 128 pages per number with the present financial arrangements; (3) that at present the Association

paid the Press 25*s.* per annum for each member as against a price of 35*s.* to subscribers outside the Association ; (4) that the Press considered that it would be unwise to increase the price to outside subscribers.

It was moved by Dr. Tidy and seconded by Sir Archibald Garrod that the contribution to the *Quarterly Journal of Medicine* should be increased by 10*s.* per annum for each member, viz. from 25*s.* to 35*s.* ; this would allow an increase of 32 pages in each number. This was carried unanimously.

Dr. Tidy gave notice that he would move next year that the subscription of each ordinary member should be increased from 30*s.* to 40*s.* per annum.

The nomination of Professor Fraser as Editor was recommended by the Executive Committee and was approved unanimously.

Scientific Business.

1. Dr. Theodore Thompson referred to 'Some Points on the Diagnosis of Spinal Tumours'.

Three cases of leptomeningeoma were described which had been successfully operated upon. The tumours were endotheliomata.

In two cases the tumours were localized by injection of lipiodol into the cisterna magna. The fluid was held up for a short time at the site of the lesion, but finally trickled through. The protein was markedly increased in one case but not in the other.

2. Dr. T. L. Hardy described two cases of acute trichiniasis which had occurred recently in Birmingham. The infection followed the consumption of roast pork. There was a well-marked eosinophilia in the blood and embryo worms were found free in the blood-stream and encysted in the muscles.

3. Dr. Ivy Mackenzie described 10 cases of leptothricosis which he had seen in the course of two years. The organism was found in the cerebro-spinal fluid, in the brain abscess, and in the blood. It appeared as small Gram-negative diplococci or diplobacilli, but gradually on culture spores were formed and non-branching filaments appeared. Several of the cases had been admitted to hospital as 'unexplained pyrexia'.

4. Sir Thomas Houston on 'The Enterococcus in relation to (*a*) Rheumatic Conditions, (*b*) Ulcerative Colitis, (*c*) Perionychia'.

The enterococcus is the same organism as the Streptococcus faecalis. It is remarkable for its resistance to heat. Several types exist, differing serologically and in carbohydrate reactions. One type has been found in certain cases of arthritis and fibrositis, and in a peculiar form of septic onychia. Another type has been repeatedly isolated from cases of ulcerative colitis, but has been isolated from other persons. Some strains are non-pathogenic. The results of injections into rabbits were described, autopsy revealing arthritis, colitis, and septic manifestations. The blood of the animal may agglutinate the organism, but agglutinins are never formed in human beings.

5. Dr. E. I. Spriggs on 'The Mortality of Abdominal Operations'. In a series of 242 abdominal operations there had been 19 deaths within six months of the operation. Of 14 cases under his own observation he thought that not more than three would be alive if no operation had been done. The series appeared to show that an abdominal operation in a person under 65, in whom there is neither preceding sepsis nor growth, is a relatively safe procedure, there being two patients only who died after such an operation.

6. Sir William Wilcox on 'Parenteric Infections'. He had seen epidemics and sporadic cases, with a fever like typhoid, with rose-spots and enlarged spleen, in which in the stools, urine, and sometimes in the blood, there were present non-lactose fermenting coliform organisms, which were not typhoid or paratyphoid bacilli. These included B. asiaticus, faecalis alkaligenes, aertrycke, Gaertner, Morgan, and others.

The patient's blood serum would usually agglutinate the bacilli. He believed that these organisms were the cause of the fever, which he termed 'parenteric fever'. Other clinical types produced by these organisms included food poisoning, irregular pyrexia with abdominal disturbances, hepatitis, and jaundice, and various infections and irregular symptoms.

Dr. Tidy did not agree with the views expressed.

7. Dr. A. Abrahams described 'Coeliac Disease in an Adult'. The patient, a woman aged 61 years, was first seen three years ago for 'colitis'. There was extreme emaciation and anaemia. The stools were bulky, frequent, and ashy-grey, containing 62 per cent. of fat, of which 72 per cent. was free fatty acid. The error was clearly one of fat malabsorption. On a rigid fat-free diet improvement was immediate, rapid, and permanent.

Dr. Ryle thought that the case was probably sprue.

The Annual Dinner was held at the Grand Central Hotel at 8 p.m. The President, Professor J. A. Lindsay, was in the Chair. The official guests included Lord Dufferin, the Lord Chief Justice, the Lord Mayor of Belfast, the Vice-Chancellor, the Recorder, and Professor A. Fullerton, P.R.C.S.I. One hundred and fifty-one members and guests were present.

Presentations were made to Sir William Hale-White in recognition of his services to the Association as Treasurer since its foundation, and to Dr. Morley Fletcher, who had been Secretary since 1919.

Saturday Morning. 10 a.m.

1. Dr. J. A. Smyth (introduced) gave an account of pre- and post-operative treatment of hyperthyroidism. Exophthalmic goitre was regarded as fundamentally different from toxic adenoma; the preparation was mainly the administration of iodine as Lugol's solution.

Immediately after operation Crooks's collosol iodine, 20 c.c., was injected subcutaneously every 4 hours. Digitalis was also given, and hypnotics. The mortality had been 6 per cent.

2. Dr. F. R. Fraser and Dr. G. C. Linder (introduced) on 'A Case of Tetany following Thyroidectomy controlled by Parathyroid Extract'. The tetany had commenced five days after sub-total thyroidectomy for exophthalmic goitre four months previously. The calcium content of the serum was low, the inorganic phosphorus high, and the carbon dioxide content high. No improvement was obtained by the injection of large doses (150 units) of Collip's parathyroid extract and the administration of calcium lactate. Following the removal of septic tonsils, and the substitution of calcium chloride for lactate, the tetany ceased. The dose of parathyroid extract was reduced to 30 units, but on stopping it entirely the tetany returned. The patient had remained free from tetany for the three months since discharge from hospital.

Professor T. K. Monro discussed this communication.

3. Dr. Hugh Thursfield recounted the case of a girl who from the age of $1\frac{1}{2}$ years had suffered from chronic infective arthritis (Still's disease). At the age of 4 years there were several joints involved, and the spleen and glands were enlarged. She became emaciated and exhausted. 'Protein shock' was then tried, the medium being T.A.B. vaccine in doses of 50, 75, and 100 millions intravenously. The pain was relieved and the progress of the disease was checked. Four years have now elapsed without any recurrence, and the glands, spleen, and joints have recovered completely.

Drs. Wilkinson, McNee, Ryle, and French discussed this communication.

4. Lord Dawson on 'Certain Aspects of Acholuric Jaundice'. He described a series of 28 cases. In 14 splenectomy was performed, of which 11 were congenital, and in 14 no operation was performed, 11 being congenital.

Of the congenital cases, of those operated upon one died within 12 hours from haemorrhage, but the others were living. Of those not operated upon, 4 had died, one from suppurative cholangitis and the others from anaemia. He recommended splenectomy as a routine.

5. Dr. Herbert French on 'Blood-letting for Plethora and raised Blood-pressure in the Middle-aged'. He urged the use of venesection in acute conditions associated with over-distension of the right heart and also in certain chronic states and in cases of splenomegalic polycythaemia.

He exhibited his needle and bottle method, the needle being of increasing bore from point to base, which reduces the liability to clotting within the needle.

Dr. Parkes Weber, Dr. Ramsbottom, and Dr. Tidy joined in the discussion.

6. Dr. J. W. McNee contributed some 'Remarks on Splenomegaly'. The first stage of Banti's disease and its characteristic histological picture was apparently not found in Great Britain, but the clinical syndrome (splenomegaly, hepatic cirrhosis, and tendency to haematemesis, &c.) described by Banti as the second stage of his disease was common, and might be termed 'Banti's Syndrome'.

Observations by Dr. M. Cashin and Dr. McNee in many lower animals were described to illustrate points in the evolutionary development of the spleen and its circulation.

As a result of this work several histologically different varieties of chronic splenomegaly in man can now be distinguished, but further work is necessary.

7. Dr. V. M. Synge described 'An Unusual Case of Pernicious Anaemia'. The patient was a woman, aged 25, whose mother had died of pernicious anaemia. The spleen was unusually large, and there was marked brown pigmentation of the skin, which commenced one year before the appearance of any other symptoms. There was no evidence of suprarenal disease.

8. Dr. W. Edgecombe and Dr. S. Miller (introduced) on 'Experiences in the Use of Colloid Lead in the Treatment of Malignant Disease'.

Eighty cases, chiefly carcinomata, had been treated. Though the period of one year was too short to permit reliable deductions to be drawn, they considered their results encouraging, and so far they had avoided serious reactions.

2–3 p.m.

Demonstration of Clinical Cases and Pathological Specimens in the Royal Victoria Hospital.

Saturday Afternoon. 3 p.m.

1. Dr. J. A. Ryle contributed 'Observations on Abdominal and Crural Angina'. He made a distinction between 'epigastric' and 'abdominal' angina, in the latter the pain being at or below the navel. He preferred the term 'angina cruris' to 'intermittent claudication', since pain of a particular type was the leading symptom. The pain of abdominal angina was probably produced in the abdominal aorta. The pain in angina cruris was also probably due to arteries rather than to the ischaemic calf muscle. Tobacco was a definite factor.

Several members took part in the discussion which followed.

2. Dr. John Parkinson and Dr. Evan Bedford (introduced) on 'Clinical Events following Coronary Thrombosis'. They had studied 96 cases. In half the cases there had been previous angina pectoris. In a typical attack of thrombosis, the pain usually lasted several hours; when severe, the distribution might be extensive, involving both arms and often the neck. Collapse, with fall of blood-pressure, vomiting, tachycardia, and fever were common. Congestive heart failure or embolism might quickly follow. The electrocardiographic changes were described; they were generally characteristic and successive changes were often diagnostic. In treatment, vasodilators were contra-indicated, morphine was essential, and digitalis was often indicated.

Drs. Hay, Parkes Weber, and Cowan discussed this communication.

3. Drs. J. E. MacIlwaine, S. B. Boyd Campbell, and S. I. Turkington (introduced) on 'Cases of Bundle Branch Block'. Fifty-six cases were reviewed. There was no constant sign or symptom, dyspnoea being the outstanding complaint. The average age of the recognition of the lesion in 30 hospital cases was 58·3 years, and in 26 private cases 63·1 years, but the hospital cases showed a death-rate of 73 per cent. as against 42 per cent. in the other series. Of the private cases four were alive after $9\frac{1}{2}$ years.

4. Dr. J. Crighton Bramwell described a case of 'Extreme Aneurysmal Dilatation of the Left Auricle', the diagnosis being made during life. The patient, a man aged 25, had suffered from rheumatic carditis since childhood. He was admitted with an attack of cardiac pain: other symptoms were slight. A systolic impulse and thrill were palpable in the right submammary region. X-ray examination showed that the heart shadow extended almost to the right chest wall. The patient died suddenly. The capacity of the left auricle was 1,080 c.c., and the initial valve was grossly incompetent. In the affected part of the auricle the muscular elements had been entirely replaced by fibrous tissue. The surprisingly good response of the heart to exercise was probably due to the brunt of the damage falling on the auricle, the ventricle being relatively healthy.

5. Dr. A. R. Parsons described cases of gout, cystinuria, and alkaptonuria.

The case of cystinuria was a woman aged 58 years who had suffered from irritability of the bladder for twenty years. No crystals were found in the urine of her only brother.

The case of alkaptonuria and ochronosis was a man aged 55 years. Pains in the knees and back had commenced eight years previously, and osseous changes were marked in these joints. The urine gave the characteristic reactions. Crystals of the homogentisate of lead were obtained with acetate of lead, and also a black powder which gave a brilliant red colour with nitric acid, possibly a condensation product of homogentisic acid and its quinone formed from the acid by oxidation.

Dr. Graham stated that homogentisic acid has never been found in the blood. The only treatment is to reduce proteins in general, since all contain the same amount of the substance. The effect of atophan is being tried.

6. Dr. C. W. Buckley described 'A Series of Investigations into the Chemistry of the Blood in Gout and Allied Diseases'. The calcium content of the serum and the hydrogen-ion concentration in tophaceous gout were within normal limits. The uric acid in the blood was increased in practically all cases.

7. Dr. S. W. Patterson on some 'Observations of the Stomach in Migraine'. He described cases in which the stomach during an attack of headache became a large motionless bag low in the abdomen, and remained full for more than twelve hours. Between attacks the stomach was observed to empty in three and a half hours. The migraine improved with measures to secure restarting of peristalsis, e. g. small doses of calomel, administration of warm alkaline fluid, or even of food.